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ان كان هناك حقوق ملكية فهي تعود للموقعين الذين اخذنا منهم المعلومات ولم يكن قصدي الا ان تعم الفائدة علي الجميع ويستطيع اخواننا الاطباء انهاء الزمالة بسهولة وفي وقت قصير وارجو ان كان هناك شبهة اني اعتديت علي ملكية هذه المواقع ارجو ان تدعو لي ان يسامحني الله فلم يكن قصدي سوا نشر العلم دون اي مقابل مادي او معنوي وكذلك انا اعتقد ان العلماء الاوائل لم نسمع ان احدا منهم منع نشر او نسخ كتبه

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Gastrointestinal physiology

Acid secretion

Principle mediators of acid secretion:

- Gastrin
- Vagal stimulation
- Histamine

Factors increasing acid secretion:

- Gastrinoma
- Small bowel resection (removal of inhibition)
- Systemic mastocytosis (elevated histamine levels)
- Basophilia

Factors decreasing acid secretion:

- Drugs: H₂-antagonists, PPIs
- Hormones: secretin, VIP, GIP, CCK

Gastrointestinal enzymes:

- Amylase is present in saliva and pancreatic secretions. It breaks starch down into sugar
- The following brush border enzymes are involved in the breakdown of carbohydrates:
 - ✓ maltase: cleaves disaccharide maltose to glucose + glucose
 - ✓ sucrase: cleaves sucrose to fructose and glucose
 - ✓ lactase: cleaves disaccharide lactose to glucose + galactose

Gastrointestinal Hormones

Below is a brief summary of the major hormones involved in food digestion:

	Source	Stimulus	Actions
Gastrin	G cells in antrum of the stomach	1) luminal peptides/amino acids 2) Distension of stomach, 3) vagus nerves mediated by gastrin-releasing peptide Inhibited by: ✓ low antral pH, ✓ somatostatin	1) Increase HCL, pepsinogen and IF secretion, 2) increases gastric motility, 3) stimulates parietal cell maturation
CCK	I cells in upper small intestine	1) Partially digested proteins and 2) Triglycerides	1) Increases secretion of enzyme-rich fluid from pancreas, 2) contraction of gallbladder and relaxation of sphincter of Oddi, 3) decreases gastric emptying, 4) trophic effect on pancreatic acinar cells, 5) induces satiety
Secretin	S cells in upper small intestine	1) Acidic chyme, 2) fatty acids	1) Increases secretion of bicarbonate-rich fluid from pancreas and hepatic duct cells, 2) decreases gastric acid secretion, 3) trophic effect on pancreatic acinar cells
VIP	Small intestine, pancreas	Neural	1) Stimulates secretion by pancreas and intestines, 2) inhibits acid secretion
Somato statin	D cells in the pancreas & stomach	Fat, bile salts and glucose in the intestinal lumen	1) Decreases acid and pepsin secretion, 2) decreases gastrin secretion, 3) decreases pancreatic enzyme secretion, 4) decreases insulin and glucagon secretion 5) inhibits trophic effects of gastrin, 6) stimulates gastric mucous production

Dysphagia

The table below gives characteristic exam question features for conditions causing dysphagia:

Oesophageal cancer	➤ Dysphagia may be associated with weight loss, anorexia or vomiting during eating ➤ Past history may include Barrett's oesophagus, GORD, excessive smoking or alcohol use
Oesophagitis	➤ May be history of heartburn ➤ Odynophagia but no weight loss and systemically well
Oesophageal candidiasis	➤ There may be a history of HIV or ➤ other risk factors such as steroid inhaler use
Achalasia	➤ Dysphagia of both liquids and solids from the start ➤ Heartburn ➤ Regurgitation of food - may lead to cough, aspiration pneumonia etc
Pharyngeal pouch	➤ More common in older men ➤ Represents a posteromedial herniation between thyropharyngeus and cricopharyngeus muscles ➤ Usually not seen but if large then a midline lump in the neck that gurgles on palpation ➤ Typical symptoms are dysphagia, regurgitation, aspiration and chronic cough. ➤ Halitosis may occasionally be seen
Systemic sclerosis	➤ Other features of CREST syndrome may be present, namely Calcinosis, Raynaud's phenomenon, oEsophageal dysmotility, Sclerodactyly, Telangiectasia ➤ As well as oesophageal dysmotility the lower oesophageal sphincter (LES) pressure is decreased. ➤ This contrasts to achalasia where the LES pressure is increased
Myasthenia gravis	➤ Other symptoms may include extraocular muscle weakness or ptosis ➤ Dysphagia with liquids as well as solids
Globus hystericus	➤ May be history of anxiety ➤ Symptoms are often intermittent and relieved by swallowing ➤ Usually painless - the presence of pain should warrant further investigation for organic causes

Pain on swallowing (odynophagia) is a typical of oesophageal candidiasis, a well documented complication of inhaled steroid therapy

Achalasia

- Failure of oesophageal **peristalsis** and of **relaxation** of lower oesophageal sphincter (LOS)
- Due to degenerative loss of ganglia from **Auerbach's plexus** i.e. LOS contracted, oesophagus above dilated.
- Achalasia typically presents in middle-age,
- rare
- Equally common in men and women.

Clinical features:

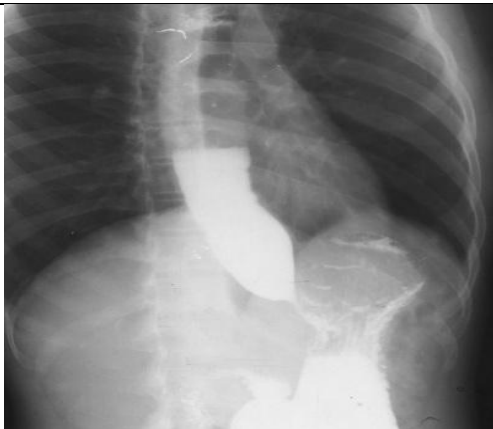
- 1) dysphagia of BOTH liquids and solids, odynophagia
- 2) typically variation in severity of symptoms
- 3) heartburn
- 4) regurgitation of food - may lead to cough, aspiration pneumonia etc
- 5) malignant change in small number of patients

Investigations:

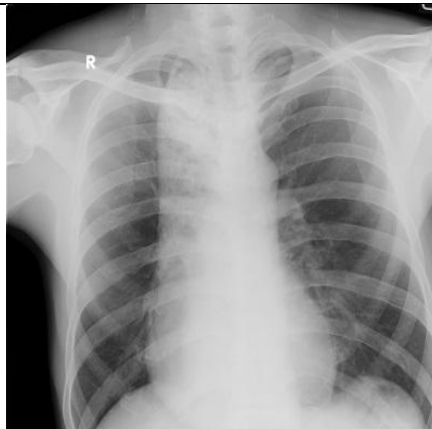
- 1) **manometry:**
 - ✓ considered **most important diagnostic test**
 - ✓ excessive LOS tone which doesn't relax on swallowing
- 2) **barium swallow** shows grossly expanded oesophagus, fluid level, 'bird's beak' appearance
- 3) **CXR:** wide mediastinum, fluid level

Treatment:

- 1) intra-sphincteric injection of **botulinum toxin**
- 2) Heller cardiomyotomy
- 3) balloon dilation
- 4) drug therapy has a role but is limited by side-effects



This film demonstrates the classical 'bird's beak' appearance of the lower oesophagus that is seen in achalasia. An air-fluid level is also seen due to a lack of peristalsis



Mediastinal widening secondary to achalasia. An air-fluid level can sometimes be seen on CXR but it is not visible on this film



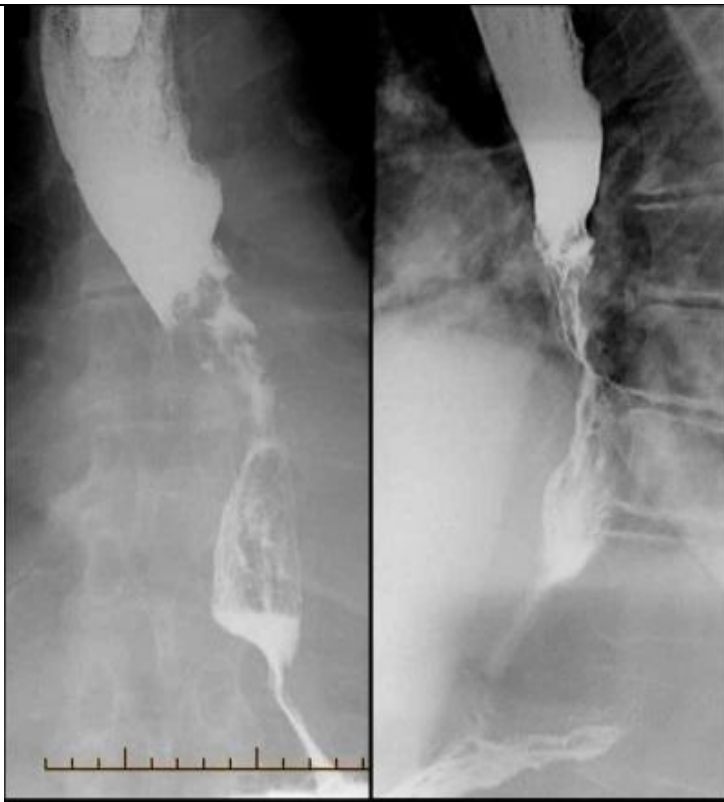
Barium swallow - grossly dilated filled oesophagus with a tight stricture at the gastroesophageal junction resulting in a 'bird's beak' appearance. Tertiary contractions give rise to a corkscrew appearance of the oesophagus

Oesophageal cancer

- Until recent times oesophageal cancer was most commonly due to a **squamous cell carcinoma** but the incidence of **adenocarcinoma** is rising rapidly.
- **Adenocarcinoma** is now the **most common** type of oesophageal cancer and is more likely to develop in patients with a history of gastro-oesophageal reflux disease (GORD) or Barrett's.
- The majority of tumours are in the middle third of the oesophagus.

Risk factors:

- 1) smoking
- 2) alcohol
- 3) GORD
- 4) Barrett's oesophagus
- 5) achalasia
- 6) Plummer-Vinson syndrome
- 7) rare: coeliac disease, scleroderma



Barium swallow - 5cm irregular narrowing of the mid-thoracic oesophagus with proximal shouldering



Fluoroscopy - a region of fixed, irregular stricturing is seen in the distal oesophagus

Pharyngeal pouch

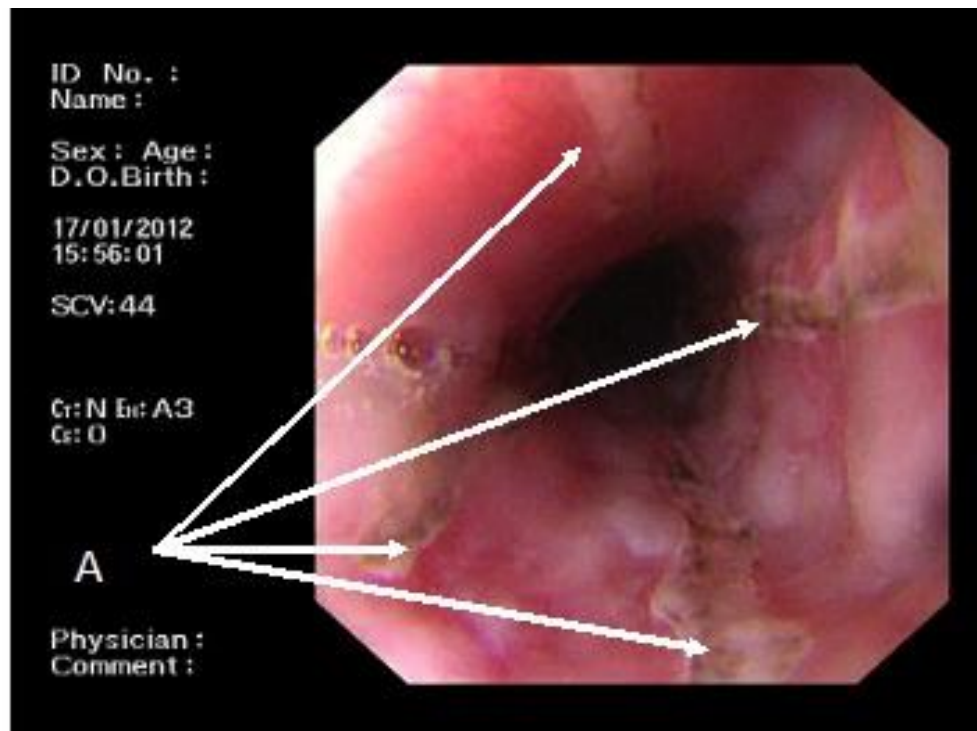
- A pharyngeal pouch is a posteromedial diverticulum through Killian's dehiscence.
- Killian's dehiscence is a triangular area in the wall of the pharynx between the thyropharyngeus and cricopharyngeus muscles.
- It is more common in older patients and
- It is 5 times more common in men.

Features:

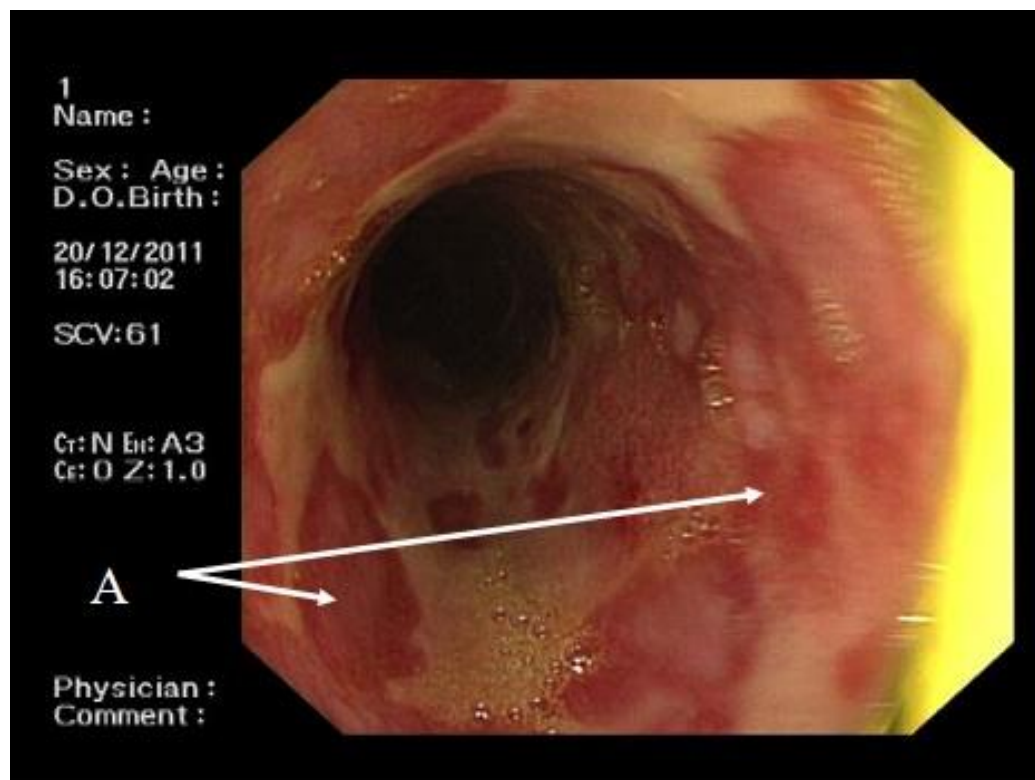
- 1) Dysphagia
- 2) Regurgitation
- 3) Aspiration
- 4) Neck swelling which gurgles on palpation
- 5) Halitosis



Still image taken from a barium swallow with fluoroscopy. During swallowing an outpouching of the posterior hypopharyngeal wall is visualised at the level C5-C6, right above the upper oesophageal sphincter



The endoscopic appearances are of four linear **oesophageal ulcers** (A) with the remainder of the oesophageal mucosa erythematous and inflamed with islands of normal mucosa.



The endoscopic appearance demonstrates severe, diffuse **oesophagitis** in the mid to distal oesophagus. **Bisphosphonates** are a well recognised cause of oesophagitis and potentially oesophageal structuring.

Dyspepsia

The main causes of dyspepsia are

- 1) Gastro-oesophageal reflux disease (GORD) (**15 - 25%**)
 - 2) Gastric and duodenal ulcers ----- (**15 - 25%**)
 - 3) Stomach cancer ----- (**2%**).
 - 4) The remaining **60%** are classified as non-ulcer dyspepsia (NUD).
-
- Patients with gastric ulceration tend to suffer from anorexia and weight loss while those with a duodenal ulcer maintain or gain weight.
 - Although weight gain may be suggestive of duodenal ulceration the characteristic clinical feature which aids the diagnosis is abdominal pain which is relieved by eating.
 - Endoscopy should be performed to confirm ulceration.
 - Risk factors for peptic ulceration include:
 - 1) Helicobacter pylori (H. pylori) infection,
 - 2) Non-steroidal anti-inflammatory drug (NSAID) use,
 - 3) cigarette smoking and
 - 4) Genetic factors - Lewis blood group antigens facilitate H. pylori attachment to the mucosa.

Dyspepsia Management:

In 2014 NICE updated their guidelines for the management of dyspepsia. These take into account the age of the patient (whether younger or **older than 55 years**) and the presence or absence of 'alarm signs':

Alarm signs

- 1) progressive unintentional **weight loss**
- 2) chronic gastrointestinal **bleeding**
- 3) progressive difficulty swallowing (**dysphagia**)
- 4) persistent **vomiting**
- 5) epigastric **mass**
- 6) iron deficiency **anaemia**
- 7) suspicious **barium meal**

Deciding whether urgent referral for endoscopy is needed:

- 1) **Urgent referral** (within 2 weeks) is indicated for patients with **any alarm signs irrespective of age**
- 2) **Routine endoscopic** investigation of patients of **any age**, presenting with dyspepsia and **without alarm signs** is not necessary
- 3) **Patients aged ≥ 55 years** should be referred **urgently** for endoscopy if dyspepsia:
 - **recent** in onset rather than recurrent and
 - **unexplained** (e.g. New symptoms which cannot be explained by precipitants such as NSAIDs) and
 - **persistent**: continuing beyond a period that would normally be associated with self-limiting problems (e.g. Up to four to six weeks, depending on the severity of signs and symptoms)

Managing patients who do not meet referral criteria ('undiagnosed dyspepsia')

This can be summarised at a step-wise approach:

- 1) **Review medications** for possible causes of dyspepsia
- 2) Lifestyle advice
- 3) **Trial of full-dose PPI for one month** OR
'Test and treat' approach for *H. pylori* using carbon-13 urea breath test

It is unclear from studies whether a trial of a PPI or a 'test and treat' should be used first

Testing for *H. pylori* infection:

1) initial diagnosis:

- ✓ NICE recommend using a **carbon-13 urea breath test** or a **stool antigen test**, or laboratory-based serology 'where its performance has been locally validated'

2) test of cure: carbon-13 urea breath test

Current NICE guidelines on the treatment of Dyspepsia (CG184) differ according to the underlying aetiology.

1) GORD

Patients with severe GORD or who have a proven pathology

(for example, oesophageal ulceration, Barrett's oesophagus)

1. Should be treated with a **healing dose of a proton pump inhibitor (PPI)** until symptoms have been controlled.
2. Once this has been achieved, the dose should be stepped down to **the lowest dose** that maintains control of symptoms.
3. A **regular maintenance** low dose of most PPIs will prevent recurrent GORD symptoms in 70-80% of patients and should be used in preference to the higher healing dose.
4. Where necessary, should symptoms re-appear, the **higher dose** should be recommenced
5. In **complicated oesophagitis** (stricture, ulcer, haemorrhage), the **full dose** should be maintained.

Patients with mild GORD symptoms and/or those who do not have a proven pathology

⇒ Can often be managed with alternative therapies including antacids, alginates, or H2 receptor antagonists

2) Documented duodenal or gastric ulcers:

1. Testing for *Helicobacter pylori* should occur.
⇒ **If positive, eradicating the infection is recommended.**
2. Long term acid-suppressing therapy is not indicated.

3) Documented NSAID-induced ulcers:

Those who must continue with NSAID therapy (e.g. those with severe rheumatoid arthritis)

- ⇒ **PPI should be prescribed.**
⇒ After the ulcer has healed, the patient should be stepped-down to a **maintenance dose PPI**

4) Non-ulcer dyspepsia (NUD):

Patients may have symptoms caused by different aetiologies

1. should not be routinely treated with PPIs
2. Should the symptoms appear to be acid-related, an **antacid** or the **lowest dose of an acid suppressor** to control symptoms should be prescribed.
3. If they do not appear to be acid-related, an alternative therapeutic strategy should be employed.

Drugs causing dyspepsia:

Causes

- NSAIDs
- bisphosphonates
- steroids

The following drugs may cause reflux

By reducing lower oesophageal sphincter (LOS) pressure

- calcium channel blockers*
- nitrates*
- theophyllines

***calcium channel blockers and nitrates are occasionally used in the management of achalasia, itself a cause of dyspepsia, because of their effect on the LOS.**

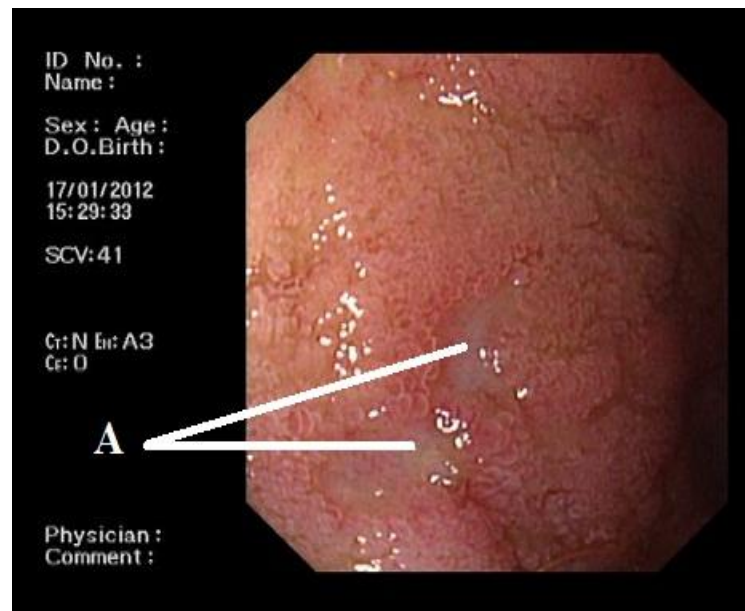


Image 1: The endoscopic appearances are of two small **duodenal ulcers** (A) without evidence of recent haemorrhage. There is some co-existent duodenitis. The presence of villi identifies this as the duodenum.

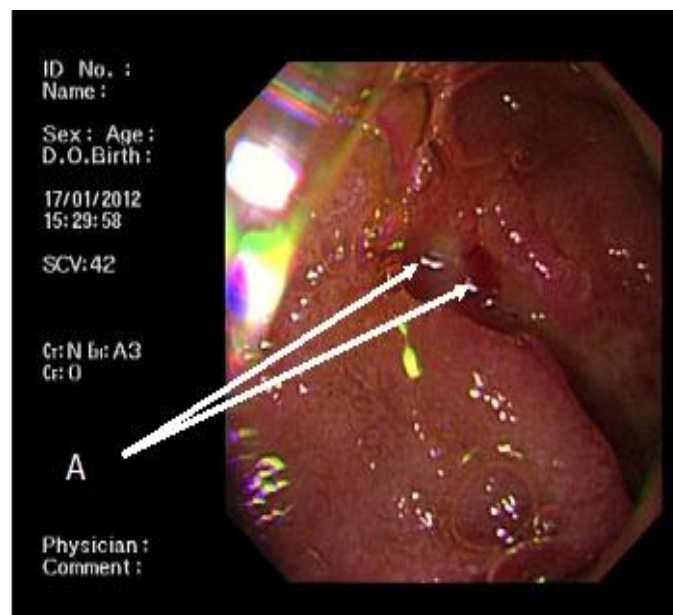


Image 2: The endoscopic appearances are of a reasonably sized duodenal ulcer (A) with evidence of recent haemorrhage and a visible vessel. There is some co-existent duodenitis. The presence of villi identifies this as the duodenum.

Helicobacter pylori

- **Gram negative bacteria**
- associated with a variety of gastrointestinal problems, principally peptic ulcer disease

Associations:

- 1) peptic ulcer disease (**95% of duodenal ulcers**, 75% of gastric ulcers)
- 2) gastric cancer
- 3) B cell lymphoma of MALT tissue
(Eradication of H pylori results causes regression in 80% of patients)
- 4) atrophic gastritis

The strongest association is with duodenal ulceration

The role of H pylori in Gastro-oesophageal reflux disease (GORD) is unclear –

There is currently no role in GORD for the eradication of H pylori

Management: - eradication may be achieved with **a 7 day course of**

- amoxicillin + a proton pump inhibitor + clarithromycin, or
- metronidazole + a proton pump inhibitor + clarithromycin

Helicobacter pylori tests:

Urea breath test:

- patients consume a drink containing carbon isotope 13 (¹³C) enriched urea
- urea is broken down by H. pylori urease
- after 30 mins patient exhale into a glass tube
- mass spectrometry analysis calculates the amount of ¹³C CO₂
- should not be performed within **4 weeks** of treatment with an antibacterial or within **2 weeks** of an antisecretory drug (e.g. a proton pump inhibitor)
- sensitivity **95-98%**, specificity **97-98%**

Rapid urease test (e.g. CLO test): *Campylobacter*-like organism

- **biopsy sample** is mixed with urea and pH indicator
- colour change if H pylori urease activity
- sensitivity **90-95%**, specificity **95-98%**

Serum antibody:

- **remains positive** after eradication
- sensitivity 85%, specificity 80%

Culture of gastric biopsy:

- provide information on antibiotic sensitivity
- sensitivity 70%, specificity 100%

Gastric biopsy:

- histological evaluation alone, no culture
- sensitivity & specificity -----> 95-99%

Stool antigen test:

- sensitivity 90%, specificity 95%
- testing may need to be delayed for three months after treatment to confirm eradication

- Eradication therapy is indicated in the context of peptic ulcer disease as it increases healing rates and reduces recurrence and is recommended by the NICE guidelines on Dyspepsia (CG184).
- The size of the respective effects is dependent upon whether ulceration is gastric or duodenal and whether the patient is taking non-steroidal anti-inflammatory drugs or not.

Gastric ulcers:

- ⇒ eradication therapy has **no effect on healing** but
- ⇒ **Decrease recurrence** (an additional 32% of patients are ulcer free at 12 months compared to acid suppression alone).

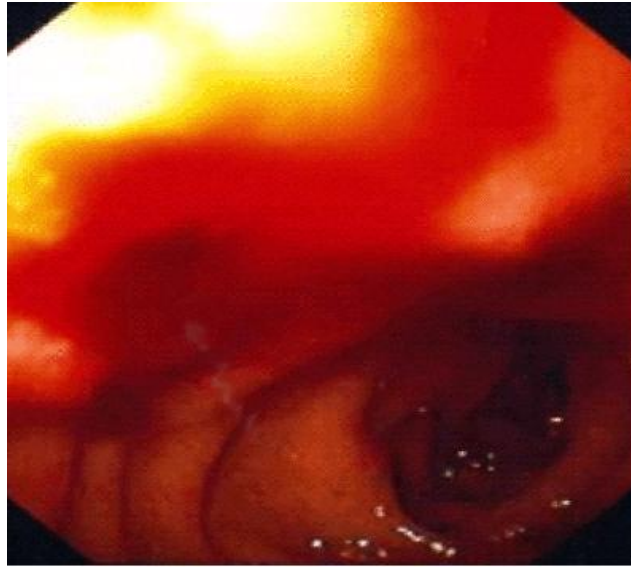
Duodenal ulcers:

- ⇒ eradication slightly **increases healing** (additional 5.4% over acid suppression alone) but
- ⇒ **Dramatically decreases recurrence** (increases the number of patients ulcer free at 12 months by 52%).

In patients taking non-steroidal anti-inflammatory drugs

- ⇒ eradication therapy has **no effect on peptic ulcer healing** (gastric or duodenal),
- ⇒ But does **reduce the chances of recurrent** peptic ulceration.
- ⇒ Continued non-steroidal anti-inflammatory drug use markedly reduces the size of effect that eradication therapy has on reducing ulcer recurrence.

- Patients with H.pylori positive and has gastritis but no ulcer, should receive a seven day course of standard eradication therapy. The absence of symptoms four weeks after eradication therapy is strong evidence that eradication has been successful.
- Confirmation of H.pylori eradication in patients who are asymptomatic at four weeks is **unnecessary** unless there has been **bleeding** or **perforation** of a peptic ulcer or where there are ongoing risk factors, for example, **anti-coagulant** or **NSAID** therapy.
- In such circumstances, the H.pylori breath test is best deferred for five weeks after the conclusion of eradication therapy.



The endoscopy shows a **bleeding duodenal ulcer** (approximately in the 9 o'clock position). The most appropriate initial step in the management of this patient is **adrenaline injection** and **heater probe application**. Peptic ulceration with stigmata of recent haemorrhage **should be treated with two modalities to achieve haemostasis** - this has been demonstrated to be significantly superior to use of only a single modality (ie adrenaline injection only) in preventing rebleeding. There is no evidence to suggest the superiority of any combination of two modalities over any other.

Studies have suggested that optimal treatment would now be to commence IV PPI for 72 hours post injection of ulcer. In particular, Lau et al. showed a decrease in recurrent bleeding, although no decrease in mortality.

Gastro-oesophageal reflux disease (GORD)

- Symptoms of oesophagitis secondary to refluxed gastric contents
- **poor correlation** between **symptoms and endoscopy appearance**
- there is currently no role in GORD for the eradication of H pylori

Investigation:

Indications for upper GI endoscopy:

- 1) age > 55 years
- 2) symptoms > 4 weeks or persistent symptoms despite treatment
- 3) dysphagia
- 4) relapsing symptoms
- 5) weight loss

If endoscopy is negative consider **24-hr oesophageal pH monitoring** (the gold standard test for diagnosis)

Management:

NICE recommend that GORD which has not been investigated with endoscopy should be treated as per the dyspepsia guidelines

1) Endoscopically proven oesophagitis:

- **full dose** proton pump inhibitor (**PPI**) for **1-2 months**
 - ⇒ if response then low dose treatment as required
 - ⇒ if no response then **double-dose** PPI for **1 month**

2) Endoscopically negative reflux disease:

- **full dose** PPI for **1 month**
 - ⇒ if response then offer low dose treatment, possibly on an as-required basis, with a limited number of repeat prescriptions
 - ⇒ if no response then **H2RA** or **prokinetic** for **one month**

Complications:

- 1) Oesophagitis
- 2) Ulcers
- 3) Anaemia
- 4) Benign strictures
- 5) Barrett's oesophagus
- 6) Oesophageal carcinoma

Barrett's oesophagus

- **Metaplasia** of the lower oesophageal mucosa,
- The usual squamous epithelium being replaced by columnar epithelium.
- There is an increased risk of oesophageal **adenocarcinoma**, estimated at **50-100** fold

Histological features:

- ☒ the columnar epithelium may resemble that of either:
 - ⇒ the cardiac region of the stomach or
 - ⇒ that of the small intestine (e.g. with goblet cells, brush border)

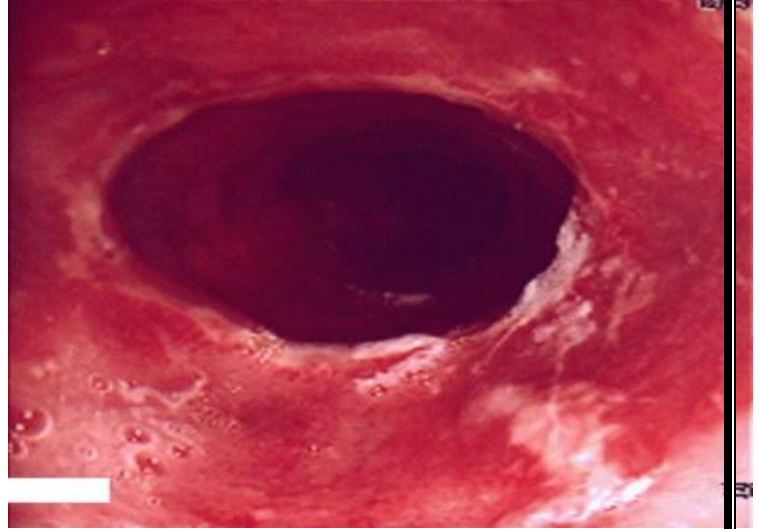


Image no 1. Endoscopy image showing a short segment of Barrett's oesophagus

Image no 2. The photograph shows a long segment of Barrett's epithelium which has replaced the normal squamous epithelium (normal mucosa seen in the bottom right corner of the photo). There is an ulcerated circumferential stricture and a linear ulcer scar extending up the oesophagus in the 5 o'clock position.

He requires biopsies to exclude dysplasia/malignancy and acid suppression with a proton pump inhibitor (PPI).

Management:

1) high-dose proton pump inhibitor:

- ⇒ whilst this is commonly used in patients with Barrett's the evidence base that this reduces the change of progression to dysplasia or induces regression of the lesion is limited

2) Endoscopic surveillance with biopsies:

1. **NO dysplasia**

- ☒ segment of Barrett's <3 cm -----> every 3 - 5 years
- ☒ Longer segment Barrett's (>3 cm) ----> (2-3 years).

2. **Low grade dysplasia:**

- ⇒ Should have high dose acid suppression and
- ⇒ Endoscopy **6 months** with biopsy until dysplastic change resolves (then as per no dysplasia) or high grade dysplasia is noted.

3. **High grade dysplasia:**

- ⇒ aggressive treatment:
 1. endoscopically (for example, **EMR** Endoscopic mucosal resection) or even
 2. **surgically** (e.g. oesophagectomy),
 3. photodynamic therapy, ablative therapy

Zollinger-Ellison syndrome

- Condition characterised by excessive levels of gastrin,
- usually from a **gastrin secreting tumour** usually of the **duodenum** or **pancreas**
- Around 30% occur as part of MEN type I syndrome

Features:

- 1) multiple gastroduodenal ulcers
- 2) diarrhoea
- 3) malabsorption

Diagnosis:

- **fasting gastrin levels**: the single best screen test
- secretin stimulation test

NB Gastrin source: from G cells in antrum of the stomach تذكر

Acute upper gastrointestinal bleeding

NICE published guidelines in **2012** on the management of acute upper gastrointestinal bleeding which is most commonly due to either peptic ulcer disease or oesophageal varices

Risk assessment:

- use the Blatchford score at first assessment, and
- the full Rockall score after endoscopy

Blatchford score:

Admission risk marker	Score
Urea (mmol/l)	6.5 – 8 = 2 8 – 10 = 3 10 - 25 = 4 > 25 = 6
Haemoglobin (g/l)	Men • 12 - 13 = 1 • 10 - 12 = 3 • < 10 = 6 Women • 10 - 12 = 1 • < 10 = 6
Systolic blood pressure (mmHg)	100 - 109 = 1 90 - 99 = 2 < 90 = 3
Other markers	Pulse $\geq 100/\text{min}$ = 1 Presentation with melaena = 1 Presentation with syncope = 2 Hepatic disease = 2 Cardiac failure = 2

Patients with a Blatchford score of 0 may be considered for early discharge

Resuscitation:

- ABC, wide-bore intravenous access * 2
- **platelet transfusion** if **actively bleeding** platelet count < **50** x $10^9/\text{litre}$
- **fresh frozen plasma** to patients who have either:
 - ⇒ a fibrinogen level <1 g/litre, or
 - ⇒ INR or APTT > 1.5 times normal
- **prothrombin complex concentrate** to patients who are taking **warfarin** and **actively bleeding**

Endoscopy:

- should be offered immediately after resuscitation in patients with a severe bleed
- all patients should have endoscopy within 24 hours

Management of **non-variceal** bleeding:

- NICE do not recommend the use of **proton pump inhibitors** (PPIs) before endoscopy to patients with suspected non-variceal upper gastrointestinal bleeding although PPIs should be given to patients with non-variceal upper gastrointestinal bleeding and stigmata of recent haemorrhage shown at endoscopy
- if further bleeding then options include repeat endoscopy, interventional radiology and surgery

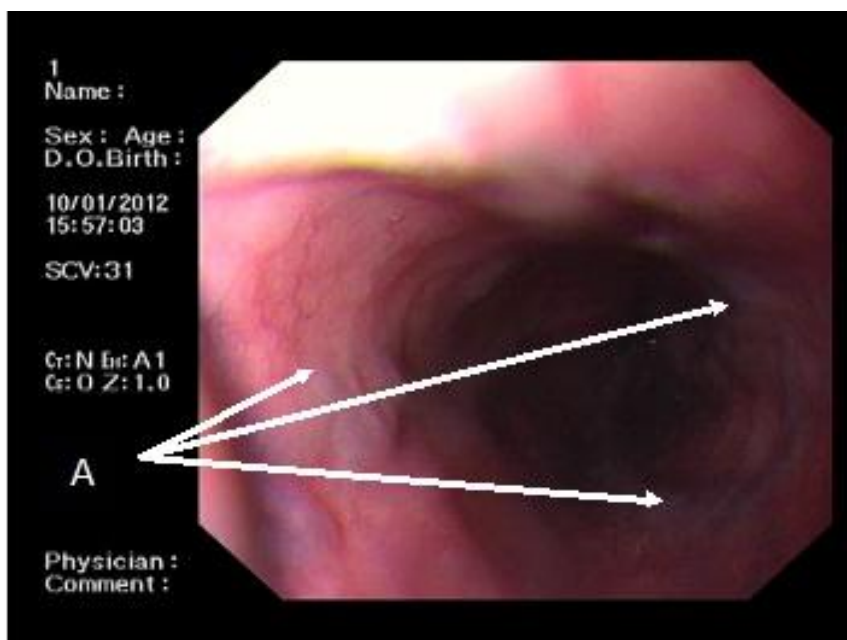
Management of **variceal** bleeding

- 1) **terlipressin** and **prophylactic antibiotics** should be given to patients at presentation (i.e. before endoscopy)
- 2) **band ligation** should be used for oesophageal varices and
- 3) **injections of N-butyl-2-cyanoacrylate** for patients with **gastric varices**
- 4) transjugular intrahepatic portosystemic shunts (**TIPS**) should be offered if bleeding from varices is not controlled with the above measures

Terlipressin and octreotide decrease portal blood pressure and have an established role in variceal haemorrhage, but not in peptic ulcer disease.

Give 2 mg IV stat followed by 1- 2 mg every four to six hours for 72 hours or until the bleeding stops. It is contraindicated in patients with known vascular disease or an ischaemic ECG.

Terlipressin helps control haemorrhage and may reduce mortality but it does not replace the necessity for endoscopy.



The endoscopic picture demonstrates a number of dilated veins running through the oesophagus, these are varices (A).

Oesophageal varices

Acute treatment of variceal haemorrhage:

- 1) ABC: patients should ideally be resuscitated prior to endoscopy
- 2) correct clotting: FFP, vitamin K
- 3) **Vasoactive agents:**
Terlipressin:
 - ✓ Is currently the only licensed vasoactive agent and is supported by NICE guidelines.
 - ✓ It has been shown to be of benefit in initial haemostasis and preventing rebleeding.
 - ✓ Octreotide may also be used although there is some evidence that terlipressin has a greater effect on reducing mortality
- 4) **prophylactic antibiotics** have been shown in multiple meta-analyses to reduce mortality in patients with liver cirrhosis
- 5) **Endoscopy:**
 - ✓ Endoscopic variceal band ligation is superior to endoscopic sclerotherapy.
 - ✓ NICE recommend band ligation
 - ✓ band ligation should be used for oesophageal varices and
 - ✓ injections of N-butyl-2-cyanoacrylate for patients with gastric varices
- 6) **Sengstaken-Blakemore tube** if uncontrolled haemorrhage
- 7) **TIPSS:** (Transjugular Intrahepatic Portosystemic Shunt) if above measures fail

Prophylaxis of variceal haemorrhage:

- 1) **Propranolol:** reduced rebleeding and mortality compared to placebo
- 2) **Endoscopic variceal band ligation (EVL)**
 - ✓ is superior to endoscopic sclerotherapy
 - ✓ It should be performed at two-weekly intervals until all varices have been eradicated.
 - ✓ Proton pump inhibitor cover is given to prevent EVL-induced ulceration

- The normal hepatic venous pressure gradient (normal HVPg = 1-5 mmHg).
- The portal hypertension is either related to:
 - ⇒ post-sinusoidal intrinsic liver disease such as cirrhosis (caused in children by metabolic disorders such as A1ATD) or
 - ⇒ Post-hepatic venous obstruction (HV thrombosis).
- The HVPg is calculated by subtracting the free hepatic venous pressure (which reflects intra-abdominal pressure) from the wedged hepatic venous pressure (which reflects portal venous pr.).
- These values are obtained by hepatic venous catheterization.
- The haemodynamic goal of treatment is reduce the HVPg by 20% or to less than 12 mmHg, using a non-selective beta blocker. If this is not achievable despite titrating the beta-blocker dose, then endoscopic variceal ligation must be considered.
- Schistosomiasis is the leading cause of pre-sinusoidal hypertension worldwide.
- Thrombosis of the portal vein is a well recognised complication in premature neonates due to cannulation of the umbilical vein during neonatal intensive care.

Gastric cancer

Epidemiology:

- overall incidence is decreasing, but incidence of tumours arising from the cardia is increasing
- peak age = 70-80 years
- more common in Japan, China, Finland and Colombia than the West
- more common in males, 2:1

Histology:

- signet ring cells may be seen in gastric cancer:
 - ✓ They contain a large vacuole of mucin which displays the nucleus to one side.
 - ✓ Higher numbers of signet ring cells are associated with a worse prognosis

Associations:

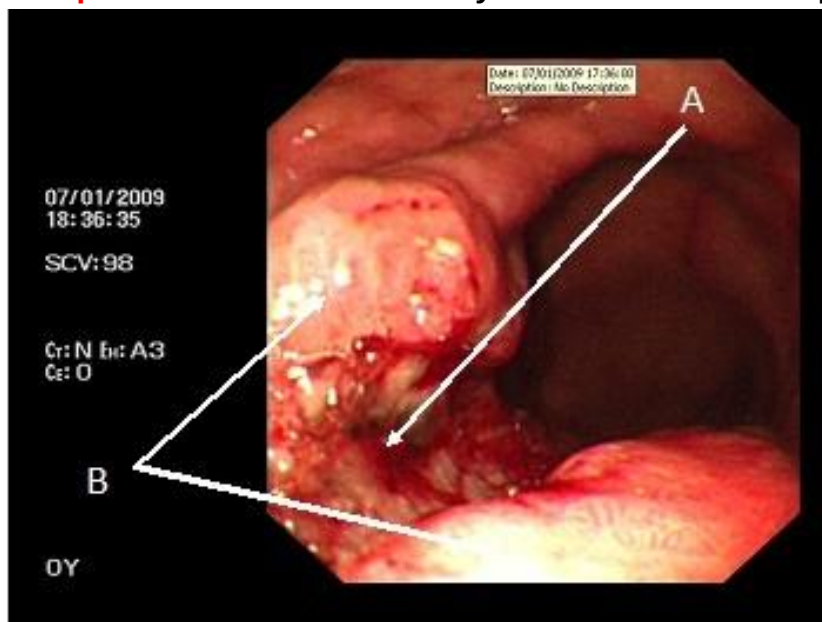
- 1) H. pylori infection
- 2) blood group A: gAstric cAncer
- 3) gastric adenomatous polyps
- 4) pernicious anaemia
- 5) smoking
- 6) diet: salty, spicy, nitrates
- 7) may be negatively associated with duodenal ulcer

Investigation:

1) Diagnosis: endoscopy with biopsy

2) Staging:

- Ct or endoscopic ultrasound –
- **Endoscopic ultrasound** has recently been shown to be superior to CT



The endoscopic picture demonstrates a large gastric ulcer and evidence of recent haemorrhage with blood visible in the ulcer crater (A). The ulcer has rolled, irregular edges with the impression of a mass at the superior aspect (B). The appearances are most consistent with **a gastric cancer**

Gastric MALT lymphoma

- Associated with H. Pylori infection in 95% of cases
- Good prognosis
- If low grade then 80% respond to H. Pylori eradication
- Paraproteinaemia may be present

Angiodysplasia

- Angiodysplasia is a vascular deformity of the gastrointestinal tract which predisposes to bleeding and iron deficiency anaemia.
- There is thought to be an association with **aortic stenosis**, although this is debated.
- Angiodysplasia is generally seen in elderly patients

Diagnosis:

- Colonoscopy
- Mesenteric angiography if acutely bleeding

Management:

- Endoscopic cautery or argon plasma coagulation
- Antifibrinolytics e.g. Tranexamic acid
- Oestrogens may also be used

Acute pancreatitis

Features:

Rare features associated with pancreatitis include:

- **ischaemic (Purtscher) retinopathy** - may cause temporary or permanent blindness

Causes:

The vast majority of cases in the UK are caused by gallstones and alcohol

Popular mnemonic is **GET SMASHED**

- Gallstones
- Ethanol
- Trauma
- Steroids
- Mumps (other viruses include Coxsackie B)
- Autoimmune (e.g. polyarteritis nodosa), Ascaris infection
- Scorpion venom
- Hyper**triglyceridaemia**, Hyper**chylomicronaemia**, Hyper**calcaemia**, Hypothermia
- ERCP (pancreatitis is the commonest complication of ERCP)
- Drugs (azathioprine, mesalazine*, didanosine, bendroflumethiazide, furosemide, pentamidine, steroids, sodium valproate)

*pancreatitis is 7 times more common in patients taking mesalazine than sulfasalazine

CRP is now a widely used marker of severity in acute pancreatitis.

Other methods which have to correlate with prognosis include the Ranson criteria and APACHE II score (Acute Physiology And Chronic Health Evaluation)

Glasgow score for Pancreatitis:

Age >55 years

PaO₂ <7.29 kPa (55)

WBC >15

Glucose >10 mmol/L

Urea >16 mmol/L

LDH >600 IU/L

Calcium <2.0 mmol/L

Albumin <32 g/L

≥ 3 criteria within first 48 hours is indicative of **severe pancreatitis**

- **Severe gallstone pancreatitis** $\Rightarrow$ **ERCP** and stone extraction within **72 hours** of onset of pain
- **Mild gallstone pancreatitis**, without cholangitis, definitive management of CBD stones on the same admission or within **2** weeks of recovery
- **PTC** (percutaneous transhepatic cholangiopancreatography) and drainage would not be indicated unless there was **cholangitis** and **failure of ERCP** to decompress the biliary system.

Chronic pancreatitis

- An inflammatory condition which can ultimately affect both the exocrine and endocrine functions of the pancreas.
- Around 80% of cases are due to **alcohol excess**
- up to 20% of cases being unexplained

Features:

- 1) **Pain:** is typically worse 15 to 30 minutes following a meal
- 2) **steatorrhoea:** symptoms of pancreatic insufficiency usually develop between 5 and 25 years after the onset of pain
- 3) **Diabetes mellitus**
 - Develops in the majority of patients.
 - It typically occurs > 20 years after symptom begin

Investigation:

- **abdominal x-ray** shows pancreatic calcification in 30% of cases
- **CT Abdomen:**
 - ⇒ **More sensitive** at detecting pancreatic calcification.
 - ⇒ Sensitivity is 80%, specificity is 85%
- functional tests: **faecal elastase** may be used to assess exocrine function if imaging inconclusive



Multiple small calcific foci projected in the pancreas consistent with chronic pancreatitis

Management:

- 1) **Pancreatic enzyme supplements**
- 2) Analgesia
- 3) Antioxidants: limited evidence base - one study suggests benefit in early disease

Pancreatic cancer

- Often **diagnosed late** as it tends to present in a non-specific way.
- Over 80% of pancreatic tumours are **adenocarcinomas** which typically occur at the **head of the pancreas**.

Associations:

- increasing age
- smoking
- diabetes
- chronic pancreatitis (alcohol does not appear an independent risk factor though)
- hereditary non-polyposis colorectal carcinoma
- multiple endocrine neoplasia
- BRCA2 gene

Features:

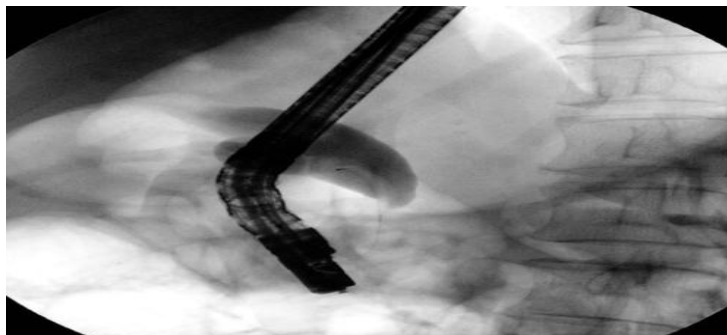
- 1) classically **painless** jaundice
- 2) however, patients typically present in a non-specific way with anorexia, weight loss, epigastric pain
- 3) loss of exocrine function (e.g. **steatorrhoea**)
- 4) atypical back pain is often seen
- 5) migratory thrombophlebitis (**Trousseau sign**) is more common than with other cancers

Investigation:

- 1) **ultrasound** has a sensitivity of around **60-90%**
- 2) **high resolution CT scanning** is the **investigation of choice** if the diagnosis is suspected

Management:

- 1) less than 20% are suitable for surgery at diagnosis
 - ⇒ **A Whipple's resection** (pancreaticoduodenectomy) is performed for resectable lesions in the head of pancreas.
 - ⇒ Side-effects of a Whipple's include dumping syndrome and peptic ulcer disease
- 2) **adjuvant chemotherapy** is usually given following surgery
- 3) **ERCP with stenting** is often used for palliation



ERCP showing invasive ductal adenocarcinoma. Note the dilation of the common bile duct due to the pancreatic lesion

Biliary System

Gallstones

Asymptomatic gallstones are common and do not require treatment

Ascending Cholangitis

- Ascending cholangitis is a **bacterial infection** of the **biliary tree**.
- The most common predisposing factor is **gallstones**.
- **Charcot's triad** of right upper quadrant (RUQ) pain, fever and jaundice occurs in about 20-50% of patients
 - fever is the most common feature, seen in 90% of patients
 - RUQ pain 70%
 - jaundice 60%
- hypotension and confusion are also common

Management:

- **Intravenous antibiotics**
- **ERCP** after **24-48 hours** to relieve any obstruction

Endoscopic retrograde cholangiopancreatography (ERCP)

Complications:

1) Pancreatitis:

- ⇒ is both the most well known and most common complication of ERCP,
- ⇒ estimates of incidence range from 1.3% to 6.7%
- ⇒ Different patient populations do have different risks of developing this complication.
- ⇒ Female sex, age less than 60 and a low probability of structural disease (suggested by a normal bilirubin, non-dilated ducts or suspected sphincter of Oddi dysfunction) all increase the risk.

2) Cholangitis:

- ⇒ is a significant risk in those with obstructive jaundice or CBD stone and
- ⇒ Occurs in around 1% of cases (estimates range from 0.5% to 5%)

3) Gastrointestinal haemorrhage:

- ⇒ reported in 0.7-2% of cases,
- ⇒ The need for biliary sphincterotomy will increase the likelihood of bleeding as a complication (1.5% in recent BSG audit data).

4) Duodenal perforation:

- ⇒ Is surprisingly common
- ⇒ estimates of incidence ranging from 0.3% to 1%

5) Cardiorespiratory complications:

- ⇒ predominantly related to sedation,
- ⇒ are a mixed group of conditions and are not infrequent (0.5-2.3%)

Gilbert's syndrome

- autosomal recessive* condition
- It is due to defective bilirubin conjugation due to a **deficiency of UDP glucuronyl transferase**
- The prevalence is approximately 1-2% in the general population

Features:

- unconjugated hyperbilinaemia (i.e. not in urine)
- jaundice may only be seen during an intercurrent illness

Investigation:

- rise in bilirubin following **prolonged fasting** or **IV nicotinic acid**

Management: no treatment required

*the exact mode of inheritance is still a matter of debate

Dubin-Johnson syndrome

- a benign **autosomal recessive** disorder
- resulting in hyperbilirubinaemia (conjugated, therefore present in urine)
- It is due to a defect in the **canillicular multispecific organic anion transporter** (cMOAT) protein.
- This causes **defective hepatic bilirubin excretion**

HIV:

The most common cause of biliary disease in patients with HIV is sclerosing cholangitis due to infections such as CMV, Cryptosporidium and Microsporidia

Pancreatitis in the context of HIV infection may be secondary to anti-retroviral treatment (especially didanosine) or by opportunistic infections e.g. CMV

Non-alcoholic fatty liver disease (NAFLD)

- The most common cause of liver disease in the developed world.
- It is largely caused by obesity and describes a spectrum of disease ranging from:
 - **Steatosis** ----- fat in the liver
 - **Steatohepatitis** ---- fat with inflammation, non-alcoholic steatohepatitis (NASH)
 - **Progressive disease** may cause **fibrosis** and liver **cirrhosis**
- NAFLD is thought to represent the hepatic manifestation of **the metabolic syndrome** and hence **insulin resistance** is thought to be the key mechanism leading to steatosis

Non-alcoholic steatohepatitis

- NASH is a term used to describe liver changes similar to those seen in alcoholic hepatitis in the absence of a history of alcohol abuse.
- It is relatively common
- affect around **3-4%** of the general population
- The progression of disease in patients with NASH may be responsible for a proportion of patients previously labelled as **cryptogenic cirrhosis**

Associated factors:

- 1) **Obesity**
- 2) **Sudden weight loss/starvation**
- 3) **Jejunioileal bypass**
- 4) Hyperlipidemia
- 5) Type 2 DM

Features:

- 1) Usually asymptomatic
- 2) Hepatomegaly
- 3) ALT is typically greater than AST **مهم**
- 4) Increased echogenicity on ultrasound

Management:

- 1) The mainstay of treatment is lifestyle changes (particularly **weight loss**) and monitoring
- 2) There is ongoing research into the role of **gastric banding** and **insulin-sensitising drugs** (e.g. Metformin)

In **alcoholic** liver disease **AST** > twice **the level of ALT**

Primary biliary cirrhosis

- A chronic liver disorder typically seen in **middle-aged females**
- Female: male ratio of **9:1**.
- The aetiology is not fully understood although it is thought to be an **autoimmune condition**.
- **Interlobular bile ducts** become damaged by a chronic inflammatory process causing progressive cholestasis which may eventually progress to **cirrhosis**.
- The classic presentation is **itching** in a middle-aged woman

Clinical features:

- 1) Early: may be asymptomatic (e.g. **raised ALP** **مهمة جدا** on routine LFTs) or **fatigue**, **pruritus**
- 2) Cholestatic jaundice (a rise in **bilirubin** is **usually a late sign**)
- 3) Hyperpigmentation, especially over pressure points
- 4) **Xanthelasmas**, **xanthomata**
- 5) Clubbing, hepatosplenomegaly, pyoderma gangrenosum
- 6) Late: may progress to liver failure

Complications:

- 1) **Malabsorption**: osteomalacia, coagulopathy (vit k deficiency)
- 2) **Sicca syndrome** occurs in **70%** of cases
- 3) **Portal hypertension**: ascites, **variceal haemorrhage**
- 4) **Hepatocellular cancer** (20-fold increased risk)

Associations:

- 1) Sjogren's syndrome (seen in up to 80% of patients)
- 2) Rheumatoid arthritis
- 3) Systemic sclerosis, Raynaud's
- 4) Thyroid disease and Addison's diseases.

Diagnosis:

- 1) Anti-mitochondrial antibodies (**AMA**) **M2 subtype** are present in **98%** of patients and are highly specific
- 2) Smooth muscle antibodies in 30% of patients
- 3) **Raised serum IgM**

Management:

- 1) Pruritus: **cholestyramine**
- 2) Fat-soluble **vitamin** supplementation
- 3) **Ursodeoxycholic acid**: It is safe and improves liver function tests, however its effect on disease progression and transplant-free survival is debated.
- 4) **Liver transplantation** very effective in PBC **5 year survival > 80%** e.g.
 - ✓ if bilirubin **> 100** (PBC is a **major indication**)
 - ✓ **recurrence** in graft can occur but is not a problem (no effect on pt. or graft **survival**)

Primary biliary cirrhosis - the M rule

- IgM
- Anti-Mitochondrial antibodies, M2 subtype
- Middle aged females

Primary sclerosing cholangitis

- A biliary disease of unknown aetiology
- Characterized by inflammation and fibrosis of **intra and extra-hepatic bile ducts**
- 80% of patients with PSC have UC

Associations:

1) Ulcerative colitis:

- 4% of patients with UC have PSC,
- 80% of patients with PSC have UC

2) Crohn's (much less common association than UC)

3) HIV

Features:

1) Cholestasis: jaundice and pruritus

2) Right upper quadrant pain

3) Fatigue

Investigation:

1) MRCP would be **the initial diagnostic investigation of choice** particularly given a lower complication rate and its ability to image ducts proximal to obstructing strictures.

2) ERCP:

- ⇒ **The GOLD standard for establishing the diagnosis**,
- ⇒ Showing multiple biliary strictures giving a '**beaded**' appearance.
- ⇒ ERCP would be reserved for cases where there is still diagnostic uncertainty or a need for therapeutic intervention.

3) pANCA may be positive **60-80%**

4) there is a **limited role** for **liver biopsy**, which may show fibrous, obliterative cholangitis often described as '**onion skin**'

Complications:

1) **Cholangiocarcinoma** (in 10%)

2) Increased risk of **colorectal cancer**

NB: Association of PSC with UC is inversely proportional to severity of symptoms of UC يعني اسهال خفيف واعراض بسيطة



ERCP shows stricturing and beading of the bile ducts, features classically seen in PSC.

Budd-Chiari syndrome

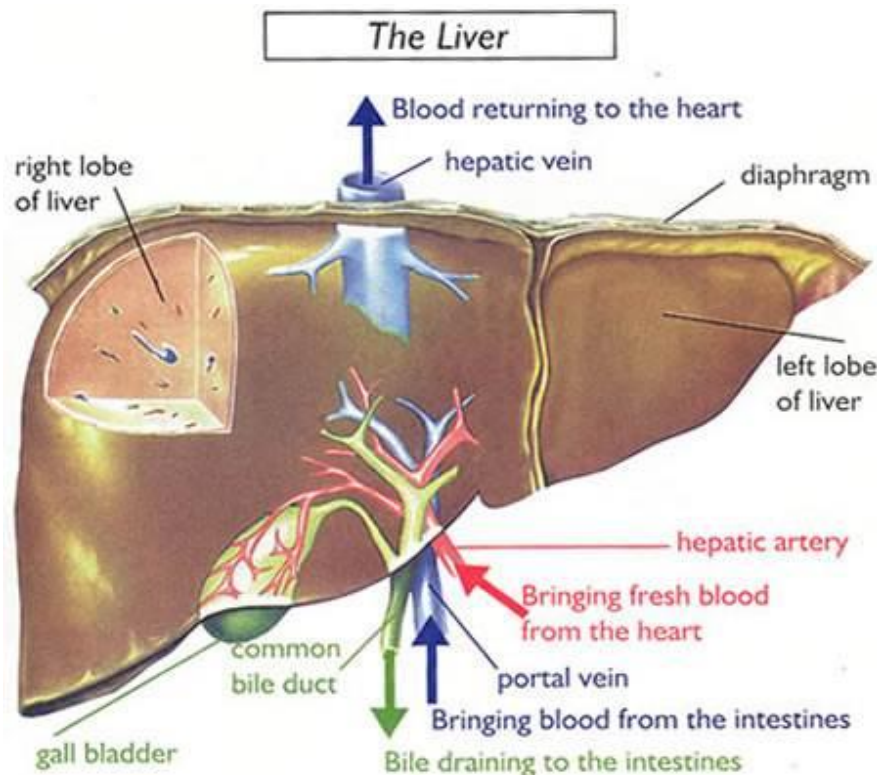
- Obstruction of the main **hepatic veins** by thrombus (may be ass. With **PNH**)
- **Abdominal pain, ascites** and **hepatomegaly** which develop over several months (rapid)
- Signs of portal hypertension, and patients may develop acute **variceal haemorrhage**
- In rare cases patients may have **acute fulminant liver failure**.
- Jaundice is variable,
- 3 year survival **50%**

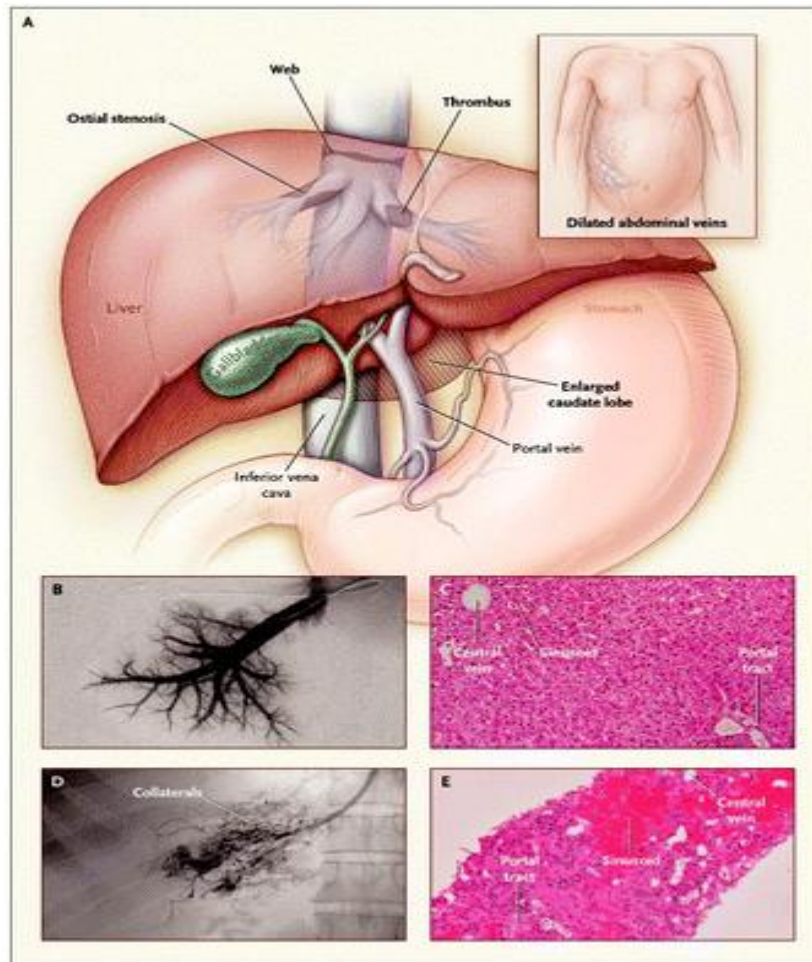
Investigations:

- 1) **Ultrasound Doppler** or **contrast CT scan** is often used Hypertrophy of the **caudate lobe** on imaging is a characteristic sign (only 50%).
- 2) Ascitic tap usually demonstrates a high SAAG (>11g/L).

MANAGEMENT:

- 1) Management of ascites and portal hypertension
- 2) **Thrombolysis** and subsequent **anticoagulation** has been used
- 3) In acute liver failure liver transplantation may be a requirement





Autoimmune hepatitis

- A condition of unknown aetiology
- Most commonly seen in **young females**
- Recognised associations include other autoimmune disorders, hypergammaglobulinaemia and HLA B8, DR3.
- Three types of autoimmune hepatitis have been characterised according to the types of circulating antibodies present

Type I	Type II	Type III
• Anti-nuclear antibodies (ANA) and/or • Anti-smooth muscle antibodies (SMA) • Affects both adults and children	• Anti-liver/kidney microsomal type 1 antibodies (LKM1) • Affects children only	• Soluble liver-kidney antigen • Affects adults in middle-age

Features:

- 1) May present with signs of chronic liver disease
- 2) Acute hepatitis: fever, jaundice etc (only 25% present in this way)
- 3) **Amenorrhoea** (common)
- 4) ANA/SMA/LKM1 antibodies,
- 5) Raised **IgG** levels
- 6) **liver biopsy**: inflammation extending beyond limiting plate '**piecemeal necrosis**', **bridging necrosis**
 {deranged LFTs + secondary amenorrhoea in a young female ----> autoimmune hepatitis}
 HLA B8, DR3>>>>also in celiac D (associated w Auto immune hepatitis) تذكر

Management:

- 1) **Steroids**
- 2) other immunosuppressants e.g. **azathioprine**
- 3) **liver transplantation**

Liver biopsy

Contraindications to percutaneous liver biopsy:

- 1) deranged clotting (e.g. **INR > 1.4**)
- 2) low **platelets** (e.g. **< 60 * 10⁹/l**)
- 3) **anaemia**
- 4) **ascites** (**either** transjugular biopsy, or ascites should be drained first)
- 5) **extrahepatic biliary obstruction**
- 6) **hydatid cyst**
- 7) **haemoangioma**
- 8) **uncooperative patient**

Wilson's disease

- An **autosomal recessive** disorder
- Characterised by **excessive copper deposition** in the tissues.
- Metabolic abnormalities include:
 - 1) **Increased copper absorption** from the small intestine and
 - 2) **Decreased hepatic copper excretion.**
- Wilson's disease is caused by a defect in the **ATP7B gene** located on **chromosome 13**.
- The onset of symptoms is usually between **10 - 25 years**.
- **Children** usually present with **liver disease**
- whereas the first sign of disease in **young adults** is often **neurological disease**

Features:

Result from **excessive copper deposition** in the tissues, especially the brain, liver and cornea:

- 1) liver: hepatitis, cirrhosis
- 2) Neurological:
 - ✓ **Speech and behavioural problems are often the first manifestations.**
 - ✓ **Basal ganglia degeneration,**
 - ✓ **Asterixis, chorea, dementia**
- 3) Kayser-Fleischer rings
- 4) renal tubular acidosis (esp. Fanconi syndrome)
- 5) haemolysis
- 6) blue nails
- 7) cardiomyopathy is a rare but recognized problem

Diagnosis:

☒ Copper studies:

- 1) reduced serum caeruloplasmin
- 2) Serum copper is paradoxically low مهمة خد بالك... النحاس قليل فى الدم....
- 3) increased 24hr urinary copper excretion

- ☒ The gold standard diagnostic test is a **liver biopsy**; however in patient who has significantly deranged clotting profile would be hazardous.

Management:

1) **Penicillamine:**

- ✓ chelates copper
- ✓ has been the traditional first-line treatment

2) **Trientine hydrochloride**

- ✓ Is an alternative chelating agent
- ✓ may become first-line treatment in the future

3) **Tetrathiomolybdate** is a newer agent that is currently under investigation

Haemochromatosis

- An **autosomal recessive disorder** of iron absorption and metabolism resulting in iron accumulation
- It is caused by inheritance of mutations in the **HFE gene** on both copies of chromosome 6*
- It is often asymptomatic in early disease and initial symptoms often non-specific e.g. lethargy and arthralgia

*there are rare cases of families with classic features of genetic haemochromatosis but no mutation in the HFE gene

Epidemiology:

- 1 in 10 people of European descent carry a mutation genes affecting iron metabolism, mainly HFE
- prevalence in people of European descent = 1 in 200

Presenting features:

- 1) Early symptoms: **fatigue**, **erectile dysfunction** and **arthralgia** (often of the hands)
- 2) 'Bronze' skin pigmentation
- 3) **Diabetes mellitus** (bronze diabetes)
- 4) Liver: stigmata of chronic liver disease, **hepatomegaly**, **cirrhosis**, hepatocellular deposition
- 5) Cardiac failure: 2nd to **dilated cardiomyopathy**
- 6) **Hypogonadism**: 2nd to cirrhosis and **pituitary dysfunction** (hypogonadotropic hypogonadism)
- 7) **Arthritis** especially of the hands

Reversible complications

- 1) Cardiomyopathy
- 2) Skin pigmentation

Irreversible complications

- 1) Liver cirrhosis
- 2) Diabetes mellitus
- 3) Hypogonadotropic hypogonadism
- 4) Arthropathy

Whilst elevated liver function tests and hepatomegaly may be reversible, cirrhosis is not.

Investigation:

- The British Committee for Standards in Haematology (BCSH) published guidelines for the investigation and management of haemochromatosis in 2000
- There is continued debate about the best investigation to **screen** for haemochromatosis.

The 2000 BCSH guidelines suggest:

1) General population:

- **Transferrin saturation** is considered the **most useful marker**.
- **Ferritin** should also be measured but is not usually abnormal in the early stages of iron accumulation

2) Testing family members: genetic testing for **HFE mutation**.

These guidelines may change as HFE gene analysis become less expensive

Diagnostic tests:

- 1) **Liver biopsy: Perl's stain**
 - ☒ **The gold standard** for the diagnosis of haemochromatosis as it quantifies iron deposition and also stages the amount of fibrosis.
- 2) **Molecular genetic testing** for the **C282Y** and **H63D** mutations
 - ☒ Ninety per cent of patients with haemochromatosis have the C282Y mutation where there is substitution of tyrosine for cysteine at position 282 of the HFE gene on chromosome 6.
 - ☒ However there is low penetrance of clinical disease and haemochromatosis also occurs in patients who are negative for this mutation.

Typical iron study profile in patient with haemochromatosis

- 1) Transferrin saturation:
 - ⇒ > 55% in men or
 - ⇒ > 50% in women
- 2) Raised ferritin (e.g. > 500 ug/l) and iron
- 3) Low TIBC

Monitoring adequacy of venesection:

BSCH recommend

- ⇒ Transferrin saturation should be kept below 50% and
- ⇒ The serum ferritin concentration below 50 ug/l'

Joint x-rays characteristically show **chondrocalcinosis**

Management:

- 1) Involves removal of body iron **by regular venesection** aiming for ferritin <50 ng/ml.
- 2) There is no role for oral or intravenous iron chelation in hereditary haemochromatosis.
- 3) Avoidance of alcohol is imperative but is not effective and consideration for **liver transplantation** is one of the long term issues to be considered.

Alkaline phosphatase (ALP)

Causes of raised alkaline phosphatase

(Source: liver, bone & placenta)

- 1) Liver: cholestasis, hepatitis, fatty liver, neoplasia
- 2) Paget's
- 3) Osteomalacia
- 4) Bone metastases
- 5) Hyperparathyroidism
- 6) Renal failure
- 7) Physiological: pregnancy, growing children, healing fractures

The table below splits the causes according to the calcium level

Raised ALP and raised calcium	Raised ALP and low calcium
1) Bone metastases 2) Hyperparathyroidism	1) Osteomalacia 2) Renal failure

Drug-Induced Liver Disease

- Generally divided into hepatocellular, cholestatic or mixed.
- There is however considerable overlap, with some drugs causing a range of changes to the liver

1) The following drugs tend to cause a hepatocellular picture:

- 1) Paracetamol
- 2) Sodium valproate, phenytoin
- 3) Anti-tuberculosis: isoniazid, rifampicin, pyrazinamide
- 4) Statins
- 5) Methyldopa
- 6) Amiodarone
- 7) Nitrofurantoin
- 8) Alcohol
- 9) MAOIs
- 10) Halothane

2) The following drugs tend to cause cholestasis (+/- hepatitis):

- 1) Oral contraceptive pill
- 2) Antibiotics: flucloxacillin, co-amoxiclav, erythromycin*
- 3) Anabolic steroids, testosterone
- 4) Phenothiazines: chlorpromazine, prochlorperazine
- 5) Sulphonylureas
- 6) Fibrates
- 7) Rare reported causes: nifedipine

*risk may be reduced with erythromycin stearate

3) Liver cirrhosis:

- 1) Methotrexate
- 2) Methyldopa
- 3) Amiodarone

Acute liver failure

A rapid onset of hepatocellular dysfunction leading to a variety of systemic complications

Causes:

- 1) Paracetamol overdose
- 2) Alcohol
- 3) Viral hepatitis (usually A or B)
- 4) Acute fatty liver of pregnancy

Features:

- 1) Jaundice
- 2) Coagulopathy: raised prothrombin time
- 3) Hypoalbuminaemia
- 4) Hepatic encephalopathy
- 5) Renal failure is common ('hepatorenal syndrome')

*remember that 'liver function tests' do not always accurately reflect the synthetic function of the liver. This is best assessed by looking at the **prothrombin time** and **albumin level**.

Hepatitis A

- Hepatitis A is typically a benign, self-limiting disease, with a serious outcome being very rare.
- Incubation period: 2-4 weeks
- RNA picornavirus
- Transmission is by faecal-oral spread, often in institutions, **uncooked shellfish**
- Doesn't cause chronic disease

Features:

- flu-like prodrome
- jaundice,
- hepatosplenomegaly

Complications:

- complications are rare and there is no increased risk of hepatocellular cancer

Immunisation:

- an effective vaccine is available
- after the initial dose a booster dose should be given 6-12 months later

Who should be vaccinated? (Based on the Green book guidelines)

- 1) people travelling to or going to reside in areas of high or intermediate prevalence, if aged > 1 year old
- 2) people with chronic liver disease
- 3) patients with haemophilia
- 4) men who have sex with men
- 5) people infected with HIV
- 6) injecting drug users
- 7) individuals at occupational risk:
 - ⇒ laboratory worker;
 - ⇒ staff of large residential institutions;
 - ⇒ sewage workers;
 - ⇒ people who work with primates قرد

Hepatitis B

- Hepatitis B is a double-stranded DNA virus and is spread through exposure to infected blood or body fluids, including vertical transmission from mother to child.
- The incubation period is 6-20 weeks.

Hepatitis B serology:

- Interpreting hepatitis B serology is a dying art form which still occurs at regular intervals in medical exams.
- It is important to remember a few key facts:

1) Surface antigen (HBsAg):

- ☒ the first marker to appear and causes the production of anti-HBs
- ☒ **HBsAg** normally implies acute disease (present for 1-6 months)
- ☒ if HBsAg is present for > 6 months then this implies chronic disease (i.e. Infective)

2) Anti-HBs:

- ☒ Implies immunity (either exposure or immunisation).
- ☒ It is negative in chronic disease

3) Anti-HBc:

- Implies previous or current infection.
- IgM anti-HBc appears during acute or recent hepatitis B infection and is present for about 6 months.
- IgG anti-HBc persists

4) HbeAg:

- ☒ results from breakdown of core antigen from infected liver cells as is therefore a marker of infectivity

Example results:

- Anti-HBs positive, all others negative previous: immunisation
- Anti-HBc positive, HBsAg negative: previous hepatitis B (> 6 months ago), not a carrier
- Anti-HBc positive, HBsAg positive: previous hepatitis B, now a carrier

Complications of hepatitis B infection:

- 1) Chronic hepatitis (5-10%).
- 2) Fulminant liver failure (1%)
- 3) hepatocellular carcinoma
- 4) glomerulonephritis
- 5) polyarteritis nodosa
- 6) cryoglobulinaemia

Management of hepatitis B:

Pegylated interferon-alpha

- ✓ used to be the only treatment available
- ✓ It reduces viral replication in up to 30% of chronic carriers.
- ✓ A better response is predicted by:
 - being female,
 - < 50 years old,
 - low HBV DNA levels,
 - non-Asian,
 - HIV negative,
 - high degree of inflammation on liver biopsy
- whilst NICE still advocate the use of pegylated interferon first-line other antiviral medications are increasingly used with an aim to suppress viral replication (not in a dissimilar way to treating HIV patients)
- examples include [tenofovir](#) and [entecavir](#)

Immunisation against hepatitis B

- contains **HBsAg** adsorbed onto aluminium hydroxide adjuvant and is prepared from **yeast cells** using **recombinant DNA technology**
- most schedules give **3 doses** of the vaccine with a recommendation for a **one-off booster 5 years** following the initial primary vaccination
- at risk groups who should be vaccinated include: healthcare workers, intravenous drug users, sex workers, close family contacts of an individual with hepatitis B, individuals receiving blood transfusions regularly, chronic kidney disease patients who may soon require renal replacement therapy, prisoners, chronic liver disease patients
- Around 10-15% of adults fail to respond or respond poorly to 3 doses of the vaccine. Risk factors include age > 40 years, obesity, smoking, alcohol excess and immunosuppression

Testing for anti-HBs:

- ⇒ Only recommended for those at risk of occupational exposure (i.e. Healthcare workers) and patients with CKD.
- ⇒ In these patients anti-HBs levels should be checked 1-4 months after primary immunization

Anti-HBs level (mIU/ml)	Response
> 100	• Indicates adequate response, no further testing required. • Should still receive booster at 5 years
10 – 100	• Suboptimal response – • one additional vaccine dose should be given • If immunocompetent no further testing is required
< 10	• Non-responder. • Test for current or past infection. • Give further vaccine course (i.e. 3 doses again) with testing following. • If still fails to respond then HBIG would be required for protection if exposed to the virus

Hepatitis B and pregnancy

- All pregnant women are offered screening for hepatitis B
- Babies born to mothers who are chronically infected with hepatitis B or to mothers who've had acute hepatitis B during pregnancy should receive:
 - ☒ a complete course of vaccination
 - +
 - ☒ hepatitis B immunoglobulin HBIG
- Studies are currently evaluating the role of oral antiviral treatment (e.g. Lamivudine) in the latter part of pregnancy
- There is little evidence to suggest C.S. reduces vertical transmission rates
- Hepatitis B cannot be transmitted via breastfeeding (in contrast to HIV)
- **Perinatal transmission** is the most common route of hepatitis B infection - the infection rate is **90%** in infants born to HBeAg positive mothers.

Hepatitis B + HIV

- Hepatitis B is fully suppressed by monotherapy with the ARV drugs, either **tenofovir** or **lamivudine**, and minimal resistance has been reported.
- **Tenofovir:**
 - ☒ A nucleoside reverse transcriptase inhibitor
 - ☒ Forms part of the first line recommended HIV treatment regime
 - ☒ So Hepatitis B can easily be suppressed during treatment for HIV.
- Some other NRTIs have partial action against Hepatitis B and could promote resistance.
- This patient has ongoing Hepatitis B as shown by the positive eAb and sAg serology and therefore there is no benefit in vaccination.
- All HIV positive patients should be offered Hepatitis B vaccination routinely using a double strength vaccination with either vaccinations at 0, 1 and 6 months or 0, 1, 2 and 12 months.

Hepatitis C

- It is likely to become a significant public health problem in the UK in the next decade.
- It is thought around 200,000 people are chronically infected with the virus.
- At risk groups include intravenous drug users and patients who received a blood transfusion prior to 1991 (e.g. haemophiliacs).

Pathophysiology:

- hepatitis C is a RNA flavivirus, incubation period: 6-9 weeks

Transmission:

- the risk of transmission during a needle stick injury -----> 2%
- the risk of transmitting the virus during sexual intercourse is probably → < 5%
- the vertical transmission rate from mother to child -----> 6%
- breast feeding is not contraindicated in mothers with hepatitis C

Features:

- after exposure to the hepatitis C virus less than 20% of patients develop an acute hepatitis

Complications:

- 1) Only 15-20% of patients will clear the virus after an acute infection and hence the majority will develop chronic hepatitis C
- 2) Chronic infection (80-85%)
- 3) Cirrhosis (20-30% of those with chronic disease)
- 4) Hepatocellular cancer
- 5) Cryoglobulinaemia, lichen planus, sjogren syndrome
- 6) Porphyria cutanea tarda (PCT): it is increasingly recognised that PCT may develop in patients with hepatitis C, especially if there are other factors such as alcohol abuse

Management of chronic infection:

- 1) currently a combination of **pegylated interferon-alpha** and **ribavirin** are used
- 2) up to 55% of patients successfully clear the virus, with success rates of around 80% for some strains
- 3) the aim of treatment is sustained virological response (SVR), defined as undetectable serum HCV RNA six months after the end of therapy

Complications of treatment:

Ribavirin side effects:

- 1) **Haemolytic anaemia, cough.**
- 2) **Teratogenic:** Women should not become pregnant within 6 months of stopping ribavirin

Interferon alpha side effects:

- flu-like symptoms, depression, fatigue, **leukopenia, thrombocytopenia**

The most important predictor of response to interferon is the genotype HCV;

- **Genotypes 2 and 3** have a far better response to treatment than genotype 1.
- Beyond this **female patients** are more likely to show a long term response to interferon.
- **The following also predict a good long term response to interferon:**
 - 1) Non-black racial origin
 - 2) Younger age
 - 3) Low hepatic iron & Absence of cirrhosis on biopsy

Hepatitis E

- RNA hepevirus
- Spread by the faecal-oral route
- incubation period: 3-8 weeks
- common in Central and South-East Asia, North and West Africa, and in Mexico
- causes a similar disease to hepatitis A, but carries a significant mortality (about 20%) **during pregnancy**
- does not cause chronic disease or an increased risk of hepatocellular cancer
- a vaccine is currently in development, but is not yet in widespread use

Pyogenic liver abscess

Management

- Drainage (needle aspiration or catheter) should always be performed
- Amoxicillin + ciprofloxacin + metronidazole
- If penicillin allergic: ciprofloxacin + clindamycin



Pyogenic hepatic abscess

Post-exposure prophylaxis

Hepatitis A

- ⇒ Human Normal Immunoglobulin (HNIG)
or
- ⇒ hepatitis A vaccine may be used depending on the clinical situation

Hepatitis B

1) HBsAg positive source:

- ☒ If the person exposed is a **known responder to HBV vaccine** then;
 - ⇒ **a booster dose** should be given
- ☒ If they are **in the process of being vaccinated** or are a **non-responder** then;
 - ⇒ **hepatitis B immune globulin (HBIG)** and
 - ⇒ **the vaccine** should be given

2) unknown source:

- ☒ for known responders the green book advises considering **a booster dose** of HBV vaccine
- ☒ For known non-responders **HBIG + vaccine** should be given
- ☒ whilst those in the process of being vaccinated should have an **accelerated course** of HBV vaccine

Hepatitis C

- monthly PCR ⇒ if seroconversion then ⇒ interferon +/- ribavirin

HIV:

- 1) A combination of oral antiretrovirals (e.g. Tenofovir, emtricitabine, lopinavir and ritonavir) ...ASAP...(i.e. Within 1-2 hours, but may be started up to 72 hours following exposure) for 4 weeks
- 2) serological testing at 12 weeks following completion of post-exposure prophylaxis
- 3) reduces risk of transmission by 80%

Varicella zoster:

- VZIG for IgG negative pregnant women/immunosuppressed

Estimates of transmission risk for single needle stick injury

Hepatitis B	20-30%
Hepatitis C	0.5-2%
HIV	0.3%

Spironolactone

Spironolactone is an aldosterone antagonist which acts in the cortical collecting duct.

Indications:

1) Ascites:

- ✓ Patients with cirrhosis develop a secondary hyperaldosteronism.
- ✓ Relatively large doses such as 100 or 200mg are often used

2) Hypertension: used in some patients as a NICE 'step 4' treatment

3) Heart failure (see RALES study below)

4) Nephrotic syndrome

5) Conn's syndrome

Adverse effects:

- Hyperkalaemia
- Gynaecomastia

RALES

- NYHA III + IV, patients already taking ACE inhibitor
- low dose spironolactone reduces all cause mortality

Hepatorenal syndrome

- The most accepted theory regarding the pathophysiology of HRS is that vasoactive mediators cause **splanchnic vasodilation** which in turn reduces the systemic vascular resistance.
- This results in 'underfilling' of the kidneys. This is sensed by the JG apparatus which then activates the RAAS, causing renal vasoconstriction which is not enough to counterbalance the effects of the splanchnic vasodilation.

Type 1 HRS	Type 2 HRS
• Rapidly progressive • Doubling of S Cr to > 221 umol/L or a halving of the Cr Cl to less than 20 ml/min over a period of less than 2 weeks • Very poor prognosis	• Slowly progressive • Prognosis poor, but patients may live for longer

Management:

- The management of hepatorenal syndrome (HRS) is notoriously difficult.
- The ideal treatment is liver transplantation but patients are often too unwell to have surgery and there is a shortage of donors

Management options:

- 1) Vasopressin analogues, for example **terlipressin**, have a growing evidence base supporting their use. They work by causing vasoconstriction of the splanchnic circulation
- 2) Volume expansion with **20% albumin**
- 3) Transjugular intrahepatic portosystemic shunt **TIPSS**

Ascites

Simple calculation:

SAAG = Serum albumin – Ascites albumin

SAAG > 11 g/L	SAAG < 11 g/L
• Cirrhosis • Alcoholic Hepatitis • Cardiac Ascites • "Mixed Ascites" • Massive Liver Metastasis • Fulminant Hepatic Failure • Budd-Chiari Syndrome • Portal Vein Thrombosis • Veno-Occlusive Disease • Myxedema • Fatty Liver of Pregnancy	• Peritoneal Carcinomatosis • Tuberculous Peritonitis • Pancreatic Ascites • Bowel Obstruction • Biliary Ascites • Nephrotic Syndrome • Postoperative Lymphatic Leak • Serositis in Connective Tissue Disease

- **The serum ascites albumin gradient (SAAG) is considered the most sensitive and specific method of categorising ascites.**
- **To calculate the ascitic fluid albumin should be subtracted from the serum albumin.**
- **A value that is ≥ 11 g/L (high SAAG) indicates a transudate (e.g. cirrhosis, cardiac failure), < 11 g/L (low SAAG) indicates an exudate (e.g. malignancy, pancreatitis).**
- **A fluid total protein cut-off level of 25 g/L has been used to categorise ascitic fluid as transudative or exudative.**

- Patients with chronic liver disease and ascites often develop hyponatraemia, the management of which can be difficult. Diuretic therapy for the management of ascites often contributes to the hyponatraemia.
- The British Society of Gastroenterology guidelines suggest that where the serum sodium is ≤ 120 mmol/L diuretic therapy should be stopped and patients should receive volume expansion with colloid or normal saline.
- These guidelines also advise that fluid restriction should only be used in patients who are clinically euvolaemic, not on diuretics and have severe hyponatraemia with a normal serum creatinine.
- No specific intervention other than careful monitoring is advised where the serum sodium is 126-135 mmol/L. In the range 121-125 mmol/L where the serum creatinine is normal, diuretic therapy may be continued but may need to be reduced with a view to stopping if necessary.
- If the sodium is in this range but the serum creatinine is rising diuretics should be stopped and patients should receive volume expansion.

Spontaneous bacterial peritonitis

A form of peritonitis usually seen in patients with ascites secondary to liver cirrhosis

Diagnosis:

- paracentesis: neutrophil **count > 250** cells/ul

Management:

- intravenous **cefotaxime** is usually given

Antibiotic prophylaxis should be given if:

- patients who have had an episode of SBP
- patients with fluid protein <15 g/l and either Child-Pugh score of at least 9 or hepatorenal syndrome

Alcoholic liver disease is a marker of poor prognosis in SBP.

An episode of spontaneous bacterial peritonitis carries **2** year mortality rate of **50%**.

Cirrhotic ascites has significantly lower protein and complement levels than non-cirrhotic ascites. This can result in less opsonic activity of the peritoneal fluid predisposing to spontaneous bacterial peritonitis.

Albumin replacement treatment is warranted in this diagnosis and can also decrease the development of the hepatorenal syndrome.

The salt poor preparation of albumin is particularly important in this scenario as high salt load will encourage fluid to shift into the extravascular compartment resulting in fluid overload.

Hepatic encephalopathy

There are 5 grades of hepatic encephalopathy:

- ✗ **Grade 0:** minimal alterations and impairment of executive function
 - ✗ **Grade 1:**
 - drowsy, sleep abnormalities (sleep inversion) and
 - Changes to behavior and personality, irritability, poor concentration.
 - ✗ **Grade 2:** Lethargy, apathy and drowsiness
 - ✗ **Grade 3:** Depressed conscious levels but rousable
 - ✗ **Grade 4:** coma with no response to painful stimuli
-
- There is little evidence for the role of protein restriction in hepatic encephalopathy. This may exacerbate the condition as these patients are often malnourished.
 - Correction of hypoglycaemia - 10% dextrose can be used but 20-50% may be required if the hypoglycaemia is severe.
 - Ensure adequate plasma expansion. Good hydration is important in preventing renal failure.
 - A full septic screen is essential including an ascitic tap if appropriate - ideally before starting empirical antibiotic therapy.
 - Patients may be critically ill and signs of sepsis may be absent. There is also a potential role for the use of antibiotics in reducing the concentration of ammoniagenic bacteria in the gut.
 - Rifaximin, a non-absorbable form of rifampicin, has been licensed for and is used in the treatment of hepatic encephalopathy.
 - Bowel cleansing reduces ammonia-producing substrates from the gut.
 - Patients should be commenced on lactulose 30-50 ml qds orally or via nasogastric tube.

Child-Pugh classification of liver cirrhosis

The Child-Pugh classification is a scoring system to assess the severity of liver cirrhosis

Score	1	2	3
Bilirubin (μ mol/l)	<34	34-50	>50
Albumin (g/l)	>35	28-35	<28
Prothrombin time, prolonged by (s)	<4	4-6	>6
Encephalopathy	None	Mild	Marked
Ascites	None	Mild	Marked

Summation of the scores allows the severity to be graded either A, B or C:

- < 7 = A
- 7-9 = B
- > 9 = C

Hepatocellular carcinoma

- The third most common cause of cancer worldwide.
- Chronic hepatitis B is the most common cause of HCC worldwide with
- Chronic hepatitis C being the most common cause in Europe.
- The main risk factor for developing HCC is liver **cirrhosis**, for example secondary to hepatitis B & C, alcohol, haemochromatosis and primary biliary cirrhosis. (Wilson's disease is an exception)

Other risk factors include:

- 1) Alpha-1 antitrypsin deficiency
- 2) Aflatoxin
- 3) Hereditary tyrosinosis
- 4) Porphyria cutanea tarda
- 5) Glycogen storage disease
- 6) Oral contraceptive pill, anabolic steroids
- 7) Male sex
- 8) Diabetes mellitus, metabolic syndrome

Features:

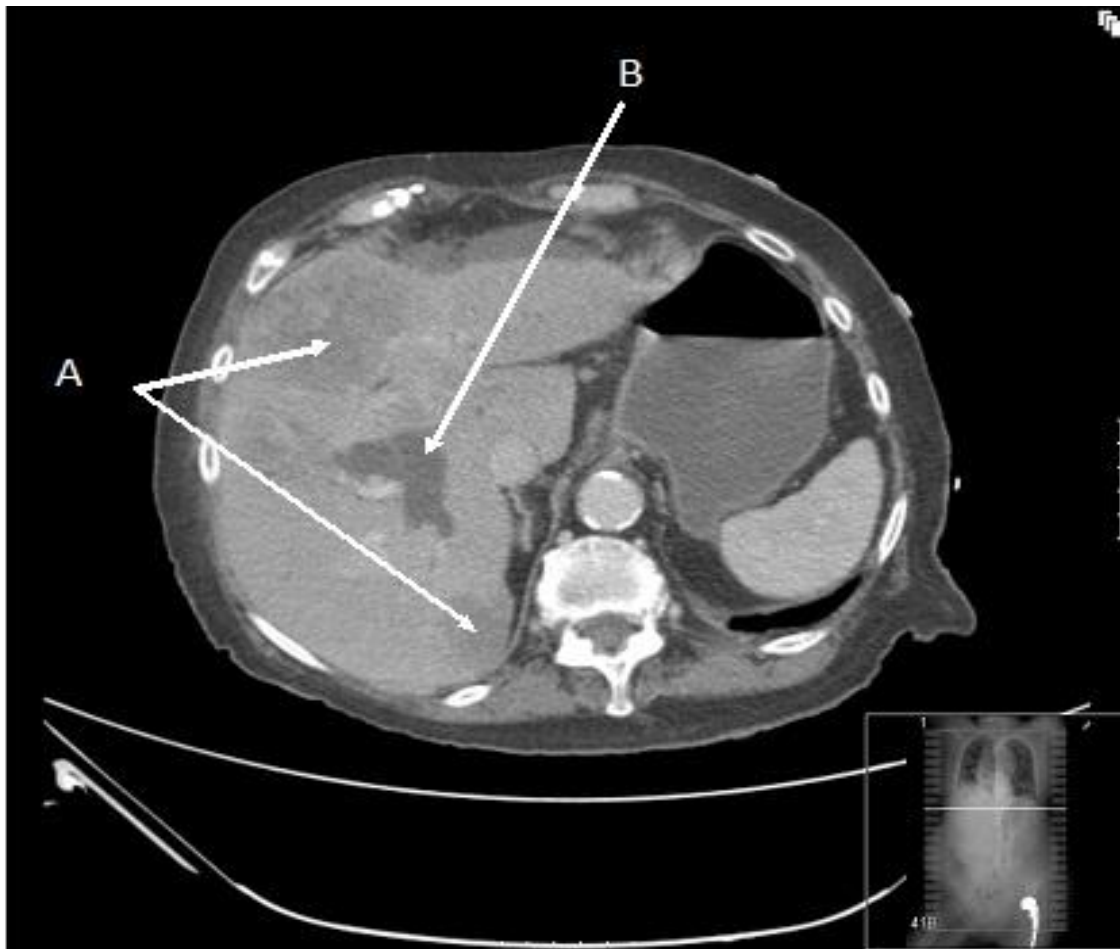
- 1) Tends to present late
- 2) Features of liver cirrhosis or failure may be seen: jaundice, ascites, RUQ pain, hepatomegaly, pruritus, splenomegaly
- 3) Possible presentation is decompensation in a patient with chronic liver disease

Screening with **ultrasound** (+/- **alpha-fetoprotein**) should be considered for high risk groups such as:

- patients liver cirrhosis secondary to hepatitis B & C or haemochromatosis
- men with liver cirrhosis secondary to alcohol

Management options:

- 1) Early disease: surgical resection
- 2) Liver transplantation
- 3) Radiofrequency ablation
- 4) Transarterial chemoembolisation
- 5) **Sorafenib**: a multikinase inhibitor



The abdominal CT demonstrates a number of ill-defined low-density deposits in the liver consistent with **hepatic metastases** (A) along with significant **intrahepatic biliary duct dilatation** (B). The likely diagnosis is metastatic pancreatic cancer causing biliary obstruction with a concomitant cholangitis.

Hepatomegaly

Common causes of hepatomegaly:

- **Cirrhosis:**
 - ✓ If early disease, later liver decreases in size.
 - ✓ Associated with a firm, non-tender liver
- **Malignancy:**
 - ✓ metastatic spread or primary hepatoma
 - ✓ Associated with a hard, irregular. liver edge
- **Right heart failure:**
 - ✓ firm, smooth, tender liver edge
 - ✓ May be pulsatile

Other causes:

- viral hepatitis
- glandular fever
- malaria
- abscess: pyogenic, amoebic
- hydatid disease
- haematological malignancies
- haemochromatosis
- primary biliary cirrhosis
- sarcoidosis, amyloidosis

Both **Dupuytren's contracture** and **parotitis** are associated with **alcoholic liver disease**. Whilst a history of alcohol excess would normally be volunteered it should be remembered many patients will lie about their alcohol intake.

Hepatosplenomegaly

Causes:

- chronic liver disease* with portal hypertension
- infections: glandular fever, malaria, hepatitis
- lymphoproliferative disorders
- myeloproliferative disorders e.g. CML
- amyloidosis

*the latter stages of cirrhosis are associated with a small liver

Splenomegaly

Massive splenomegaly

- 1) Myelofibrosis
- 2) Chronic myeloid leukaemia
- 3) Visceral leishmaniasis (kala-azar)
- 4) Malaria
- 5) Gaucher's syndrome

Other causes (as above plus):

- 1) Portal hypertension e.g. Secondary to cirrhosis
- 2) Lymphoproliferative disease e.g. CLL, Hodgkin's
- 3) Haemolytic anaemia
- 4) Infection: hepatitis, glandular fever
- 5) Infective endocarditis
- 6) sickle-cell*, thalassaemia
- 7) Rheumatoid arthritis (Felty's syndrome)

*the majority of adult patients with sickle-cell will have an atrophied spleen due to repeated infarction

Coeliac disease

- Coeliac disease is caused by a T cell mediated hypersensitivity reaction to gluten which causes intestinal inflammation and atrophy.
- Repeated exposure leads to **villous atrophy** which in turn causes **malabsorption**.
- Conditions associated with coeliac disease include:
 - 1) **Dermatitis herpetiformis** (a vesicular, pruritic skin eruption) and
 - 2) Aphthous mouth ulceration
 - 3) **Autoimmune disorders** (type 1 DM and autoimmune hepatitis)
- It is strongly associated with **HLA-DQ2** (95% of patients) and **HLA-B8** (80%) as well as **HLA-DR3** and **HLA-DR7**

In 2009 NICE issued guidelines on the investigation of coeliac disease

They suggest that the following patients should be screened for coeliac disease:

Signs and symptoms	Conditions
• Chronic or intermittent diarrhoea • Persistent or unexplained gastrointestinal symptoms including nausea and vomiting • Recurrent abdominal pain, cramping or distension • Failure to thrive or faltering growth (in children) • Prolonged fatigue ('tired all the time') • Sudden or unexpected weight loss • Unexplained iron-deficiency anaemia, or other unspecified anaemia	1) Autoimmune thyroid disease 2) Type 1 diabetes 3) Dermatitis herpetiformis 4) Irritable bowel syndrome 5) First-degree relatives (parents, siblings or children) with coeliac disease

Complications:

- 1) Anaemia:
 - ✓ iron, folate and vitamin B12 deficiency
 - ✓ folate deficiency is more common than vitamin B12 deficiency in coeliac disease
- 2) Osteoporosis, osteomalacia
- 3) **Hyposplenism**
- 4) Lactose intolerance
- 5) Subfertility,
- 6) Unfavourable pregnancy outcomes
- 7) Enteropathy-associated T-cell lymphoma of small intestine
- 8) Rare: oesophageal cancer, other malignancies

Coeliac disease investigation:

- Diagnosis is made by a combination of immunology and jejunal biopsy.
- Villous atrophy and immunology normally reverses on a gluten-free diet.
- NICE issued guidelines on the investigation of coeliac disease in 2009.
- If patients are already taking a gluten-free diet they should be asked, if possible, to reintroduce gluten for at least **6 weeks** prior to testing.

1) Immunology:

- **Tissue transglutaminase (TTG) antibodies** (IgA) are **first-choice** according to NICE
- **Endomyseal antibody** (IgA) 90% sensitive and almost **100% specific**
- Anti-gliadin antibody (IgA or IgG) tests are **not recommended** by NICE
- Anti-casein antibodies are also found in some patients

2) Jejunal biopsy:

- Biopsies from the second part of the duodenum
- villous atrophy
- crypt hyperplasia
- increase in intraepithelial **lymphocytes**
- lamina propria infiltration with **lymphocytes**

3) Rectal gluten challenge: has been described but is not widely used

- ☒ Selective IgA deficiency may lead to false negative coeliac antibody tests
- ☒ It is common in Caucasian (1:1000), it is much more common in individuals with atopic or autoimmune disease. So, **Measure serum immunoglobulins prior to measure IgG versions of the antibodies TTG**

Coeliac disease management:

- The management of coeliac disease involves a gluten-free diet.
- **Gluten containing cereals include:**
 - wheat: bread, pasta, pastry القمح: الخبز والمعكرونة والمعجنات
 - barley*: beer الشعير : البيرة
 - rye حبوب الجاودار (تشبه القمح ويصنع منها الويسكي)
 - oats** الشوفان

Some notable foods which are gluten-free include:

- Rice
- Potatoes
- Corn (maize) الذرة

Tissue transglutaminase antibodies may be checked to check compliance with a gluten free diet.

*whisky is made using malted barley. Proteins such as gluten are however removed during the distillation process making it safe to drink for patients with coeliac disease

**some patients with coeliac disease appear able to tolerate oats

Jejunal villous atrophy

Whilst coeliac disease is the classic cause of jejunal villous atrophy there are a number of other causes you need to be aware of

Causes:

- 1) Coeliac disease**
- 2) Tropical sprue**
- 3) Whipple's disease**
- 4) Cow's milk intolerance**
- 5) Hypogammaglobulinaemia**
- 6) Gastrointestinal lymphoma**

Irritable bowel syndrome diagnosis

- NICE published clinical guidelines on the diagnosis and management of irritable bowel syndrome (IBS) in 2008
- **The diagnosis of IBS** should be considered if pt has had the following for at least **6 months**:
 - abdominal pain, and/or
 - bloating, and/or
 - change in bowel habit

A positive diagnosis of IBS should be made if:

- ⇒ the patient has abdominal pain relieved by defecation or
- ⇒ associated with altered bowel frequency stool form,
- ⇒ in addition to 2 of the following 4 symptoms:
 - 1) Altered stool passage (straining, urgency, incomplete evacuation)
 - 2) Abdominal bloating (more common in women than men), distension, tension or hardness
 - 3) Symptoms made worse by eating
 - 4) Passage of mucus
- Features such as **lethargy**, **nausea**, **backache** and **bladder symptoms** may also support the diagnosis

Red flag features should be enquired about:

- rectal bleeding
- unexplained/unintentional weight loss
- family history of bowel or ovarian cancer
- onset after 60 years of age

Suggested primary care investigations are:

- full blood count
- ESR/CRP
- coeliac disease screen (tissue transglutaminase antibodies)

Irritable bowel syndrome management:

- The management of irritable bowel syndrome (IBS) is often difficult and varies considerably between patients.
- NICE issued guidelines in 2008

A. First-line pharmacological treatment - according to predominant symptom:

- pain: antispasmodic agents
- constipation: laxatives but avoid lactulose
- diarrhoea: loperamide is first-line

B. Second-line pharmacological treatment:

- **low-dose TCA** (e.g. amitriptyline 5-10 mg) are used in preference to selective serotonin reuptake inhibitors SSRI

C. Other management options:

1) psychological interventions:

- ✓ if symptoms do not respond to pharmacological treatments after **12 months** and who develop a continuing symptom profile (**refractory IBS**),
- ✓ consider referring for:
 - cognitive behavioural therapy,
 - hypnotherapy or
 - psychological therapy

2) complementary and alternative medicines: 'do not encourage use of acupuncture or reflexology for the treatment of IBS'

D. General dietary advice:

- have regular meals and take time to eat
- avoid missing meals or leaving long gaps between eating
- drink at least 8 cups of fluid per day, especially water or other non-caffeinated drinks such as herbal teas
- restrict tea and coffee to 3 cups per day
- reduce intake of alcohol and fizzy drinks
- consider **limiting intake** of high-fibre food for example,
 - ⇒ wholemeal or high-fibre flour and breads,
 - ⇒ cereals high in bran, and
 - ⇒ whole grains such as brown rice
- reduce intake of 'resistant starch' often found in processed foods
- limit fresh fruit to 3 portions per day
- for diarrhoea, avoid sorbitol
- for wind and bloating consider increasing intake of:
 - ⇒ **oats** (for example, oat-based breakfast cereal or porridge) and
 - ⇒ **linseeds** بذر الكتان (up to one tablespoon per day)

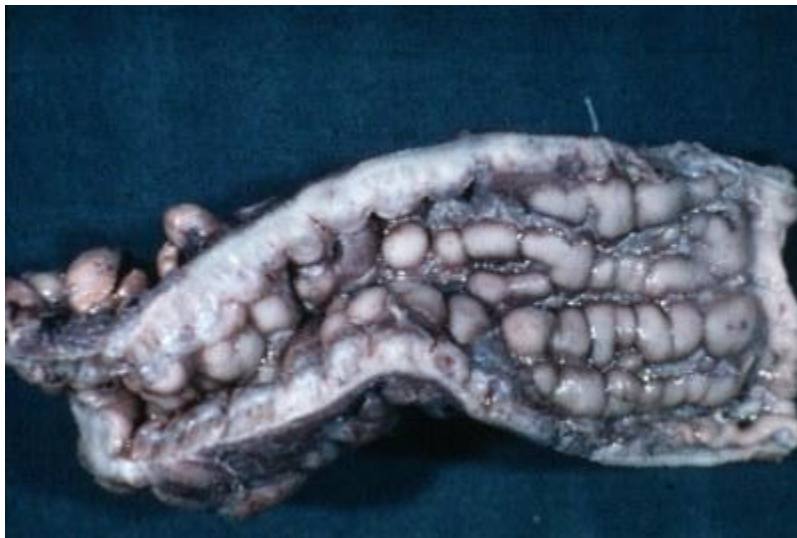
Inflammatory Bowel (IBD)

Histology:

These histological differences between ulcerative colitis and Crohn's are summarised below:

Crohn's:

- Inflammation occurs in all layers, down to the serosa. This predisposes to strictures, fistulas and adhesions
- Oedema of mucosa and submucosa, combined with deep fissured ulcers ('rose-thorn') leads to a 'cobblestone' pattern
- Lymphoid aggregates
- Non-caseating granulomas
- Increased goblet cells



A section of excised bowel

The picture shows the typical 'cobblestone mucosa' of Crohn's disease with isolated areas of normal mucosa surrounded by deep ulceration (ulcerative colitis does not result in such deep ulceration).

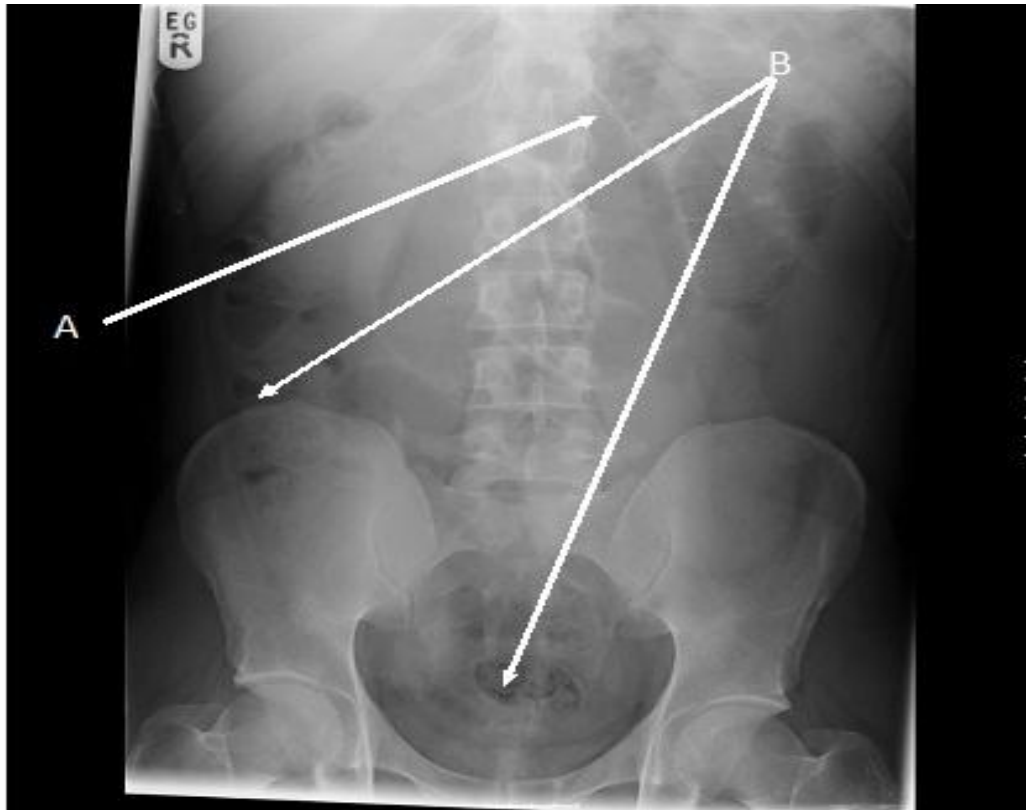
Ulcerative colitis:

- red, raw mucosa, bleeds easily
- inflammation in mucosa and submucosa only (unless fulminant disease)
- widespread ulceration with preservation of adjacent mucosa which has the appearance of polyps ('pseudopolyps')
- **neutrophils** migrate through the walls of glands to form **crypt abscesses** (Remember in **celiac** → **intraepithelial** and **lamina propria lymphocytes infiltration**)
- inflammatory cell infiltrate in lamina propria
- granulomas are infrequent
- depletion of goblet cells and mucin from gland epithelium

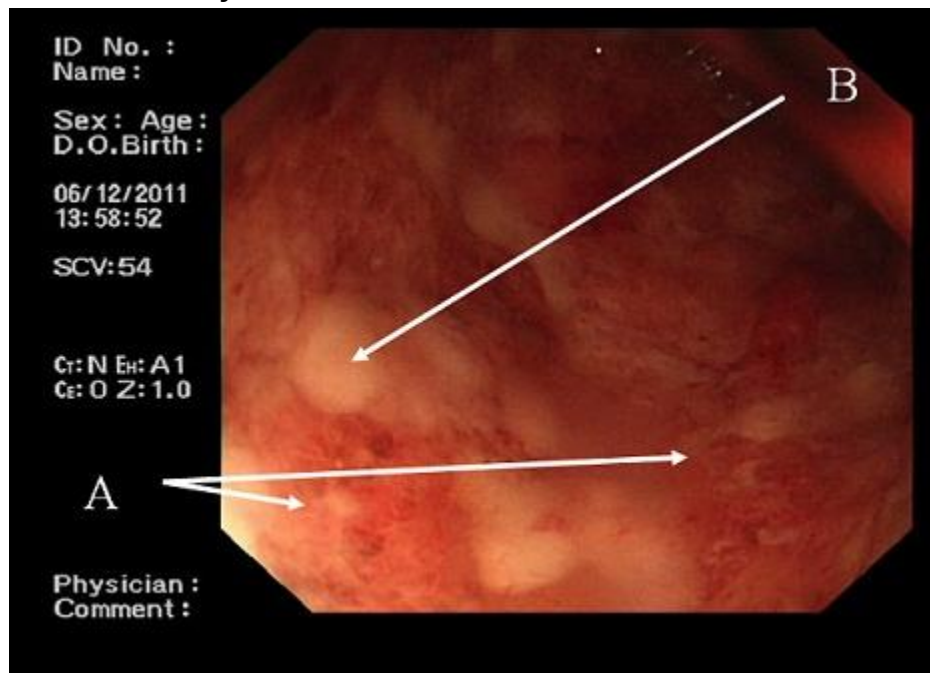
Key differences:

	Crohn's disease (CD)	Ulcerative colitis (UC)
Features	- Diarrhoea usually non-bloody - Weight loss more prominent - Upper gastrointestinal symptoms - mouth ulcers, perianal disease - Abdominal mass palpable in the right iliac fossa	Bloody diarrhoea more common - Abdominal pain in the left lower quadrant - Tenesmus
Extra-intestinal	Gallstones are more common secondary to reduced bile acid reabsorption Oxalate renal stones*	Primary sclerosing cholangitis more common ⇒ 4% of patients with UC have PSC, ⇒ 80% of patients with PSC have UC
Complications	Obstruction, fistula, colorectal cancer	Risk of colorectal cancer high in UC than CD
Pathology	✓ Lesions may be seen anywhere from the mouth to anus ✓ Skip lesions may be present	✓ Inflammation always starts at rectum and never spreads beyond ileocaecal valve ✓ Continuous disease
Histology	Inflammation in all layers from mucosa to serosa - increased goblet cells - granulomas	No inflammation beyond submucosa (unless fulminant disease) inflammatory cell infiltrate in lamina propria: - neutrophils migrate through the walls of glands to form crypt abscesses - depletion of goblet cells and mucin from gland epithelium - granulomas are infrequent
Endoscopy	Deep ulcers, skip lesions - ' cobble-stone ' appearance	Widespread ulceration with preservation of adjacent mucosa which has the appearance of polyps (' pseudopolyps ')
Radiology	<u>Small bowel enema:</u> - high sensitivity and specificity for examination of terminal ileum 1) strictures: 'Kantor's string sign' 2) proximal bowel dilation 3) 'rose thorn' ulcers 4) Fistulae	<u>Barium enema:</u> - loss of haustrations - superficial ulceration, 'pseudopolyps' - long standing disease: ⇒ colon is narrow and short 'drainpipe colon'

*impaired bile acid reabsorption increases the loss calcium in the bile. Calcium normally binds oxalate.



The abdominal x ray demonstrates a number of loops of distended small bowel in the left upper quadrant (A) (small bowel is not normally visible on abdominal films unless dilated). There is a small amount of faecal residue in the ascending colon and rectum (B) however there is generally a paucity of large bowel gas and the colon appears collapsed down. Appearances are consistent with small bowel obstruction and in view of the patient's age and lack of previous surgery the most likely diagnosis is a stricture secondary to **Crohn's disease**.



The endoscopic appearance (picture taken in the sigmoid colon) demonstrates severe, diffuse ulceration and inflammation of the colonic mucosa (A). The bowel is oedematous and featureless. There are islands of relatively preserved mucosa (B) which give an appearance of polyps due to the surrounding ulceration.

Ulcerative colitis

Crohn's disease

- A form of inflammatory bowel disease.
- It commonly affects the **terminal ileum** and **colon** but may be seen anywhere from the mouth to anus.
- Crohn's disease typically presents in late adolescence or early adulthood.

Pathology:

- cause is unknown but there is a strong genetic susceptibility
- Inflammation occurs in all layers, down to the serosa. This is why patients with Crohn's are prone to strictures, fistulas and adhesions

Features include:

- 1) presentation may be non-specific symptoms such as weight loss and lethargy
- 2) diarrhea (**Non bloody**):
 - ✓ the most prominent symptom in adults
 - ✓ Crohn's **colitis** may cause **bloody** diarrhoea
- 3) abdominal pain: the most prominent symptom in children
- 4) perianal disease: e.g. Skin tags or ulcers
- 5) extra-intestinal features are more common in patients with colitis or perianal disease

Questions regarding the 'extra-intestinal' features of inflammatory bowel disease are common:

	Common to both Crohn's disease (CD) and Ulcerative colitis (UC)	Notes
Related to disease activity	1) Arthritis: ⇒ pauciarticular, ⇒ asymmetric 2) Erythema nodosum 3) Episcleritis 4) Osteoporosis	Arthritis: ⇒ the most common extra-intestinal feature in both CD and UC Episcleritis ⇒ more common in CD
Unrelated to disease activity	1) Arthritis: ⇒ polyarticular, ⇒ symmetric 2) sacroilitis 3) Uveitis 4) Pyoderma gangrenosum 5) Clubbing 6) Primary sclerosing cholangitis	Primary sclerosing cholangitis ⇒ much more common in UC Uveitis ⇒ more common in UC

Crohn's disease investigation:

Bloods:

- C-reactive protein correlates well with **disease activity**

Endoscopy:

- **colonoscopy** is the **investigation of choice**
- features suggest of Crohn's include **deep ulcers**, **skip lesions** & '**cobble-stone**'

Histology:

- inflammation in all layers from mucosa to serosa
- oedema of mucosa and submucosa, combined with deep fissured ulcers ('rose-thorn') leads to a 'cobblestone' pattern
- **lymphoid** aggregates
- non-caseating **granulomas**
- **increased** goblet cells

Small bowel enema:

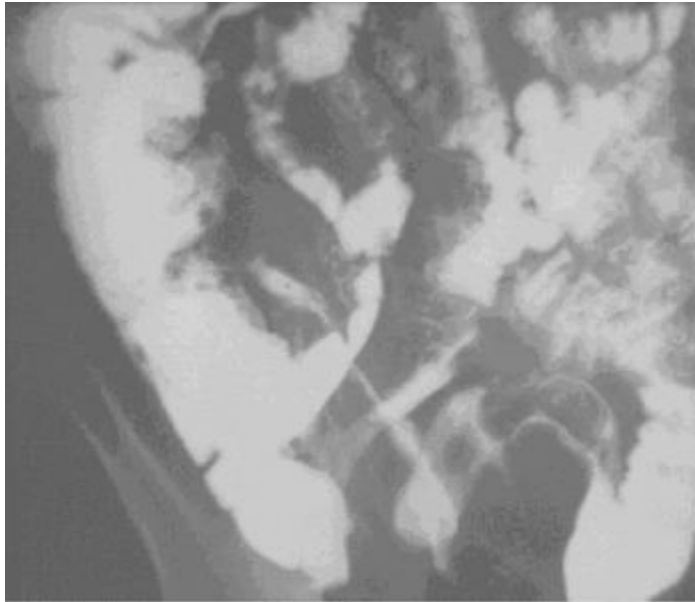
- high sensitivity and specificity for examination of the terminal ileum
- strictures: 'Kantor's string sign'
- proximal bowel dilation
- 'rose thorn' ulcers
- Fistulae



'Kantor's string sign'



Rose thorn ulcer



Crohn's disease

Crohn's disease management:

NICE published guidelines on the management of Crohn's disease in 2012. General points:

- patients should be strongly advised to **stop smoking**
- some studies suggest an increased risk of **relapse** secondary to **NSAIDs** and the **combined oral contraceptive pill** but the evidence is patchy

Inducing remission:

1) Glucocorticoids

- ✓ oral, topical or intravenous are generally used to induce remission
- ✓ Budesonide is an alternative in a subgroup of patients

2) Enteral feeding with an elemental diet

- ✓ may be used in addition to or instead of other measures to induce remission, particularly if there is concern regarding the side-effects of steroids (for example in young children)

3) 5-ASA drugs (e.g. mesalazine)

- ✓ are used second-line to glucocorticoids but are not as effective

4) Azathioprine or mercaptopurine

- ✓ may be used as an add-on medication to induce remission but is not as monotherapy
- ✓ assess **thiopurine methyltransferase (TPMT)** activity before offering azathioprine or mercaptopurine
- ✓ **Methotrexate** is an alternative to azathioprine

5) Infliximab

- ✓ is useful in **refractory** disease and **fistulating** Crohn's,
- ✓ Patients typically continue on azathioprine or methotrexate. (Used also in rheumatoid arthritis)

6) Metronidazole is often used for isolated peri-anal disease

Maintaining remission:

1) Stopping smoking

Is a priority (remember: smoking makes crohn's worse, but may help ulcerative colitis)

2) Azathioprine or mercaptopurine is used **first-line** to maintain remission

3) Methotrexate is used **second-line**

4) 5-ASA drugs (e.g. mesalazine) should be considered if a patient has had previous surgery

Surgery:

- around 80% of patients with Crohn's disease will eventually have surgery

Ulcerative colitis

- Inflammation always starts at **rectum** (hence it is the most common site for UC),
- Never spreads beyond ileocaecal valve and is continuous
- The peak incidence of ulcerative colitis is in people aged **15-25 yr** and in those aged **55-65** yr.
- The initial presentation is usually following insidious and intermittent symptoms.

Features include:

- 1) Bloody diarrhoea
- 2) Urgency
- 3) Tenesmus
- 4) Abdominal pain, particularly in the left lower quadrant
- 5) Extra-intestinal features (see below)

	Common to both Crohn's disease (CD) and Ulcerative colitis (UC)	Notes
Related to disease activity	5) Arthritis: ⇒ pauciarticular, ⇒ asymmetric 6) Erythema nodosum 7) Episcleritis 8) Osteoporosis	Arthritis: ⇒ the most common extra-intestinal feature in both CD and UC Episcleritis ⇒ more common in CD
Unrelated to disease activity	7) Arthritis: ⇒ polyarticular, ⇒ symmetric 8) sacroilitis 9) Uveitis 10) Pyoderma gangrenosum 11) Clubbing 12) Primary sclerosing cholangitis	Primary sclerosing cholangitis ⇒ much more common in UC Uveitis ⇒ more common in UC

Pathology:

- Red, raw mucosa, bleeds easily
- No inflammation beyond submucosa (unless fulminant disease)
- Widespread ulceration with preservation of adjacent mucosa which has the appearance of polyps ('**pseudopolyps**')
- Inflammatory cell infiltrate in lamina propria
- Neutrophils migrate through the walls of glands to form **crypt abscesses**
- Depletion of goblet cells and mucin from gland epithelium
- Granulomas are infrequent

Barium enema

- Loss of haustrations
- Superficial ulceration, 'pseudopolyps'
- Long standing disease: colon is narrow and short -'**drainpipe colon**'

Ulcerative colitis: colorectal cancer

- risk of colorectal cancer is 10-20 times that of general population
- the increased risk is mainly related to chronic inflammation
- worse prognosis than patients without ulcerative colitis (partly due to delayed diagnosis)
- lesions may be multifocal

Factors increasing risk of cancer:

- 1) disease duration > 10 years
- 2) onset before 15 years old
- 3) patients with pancolitis
- 4) unremitting disease
- 5) poor compliance to treatment

Ulcerative colitis management:

- Treatment can be divided into inducing and maintaining remission.
- NICE released guidelines on the management of ulcerative colitis in 2013.

The severity of UC is usually classified as being mild, moderate or severe:

- Mild: < 4 stools/day, only a small amount of blood
- Moderate: 4-6 stools/day, varying amounts of blood, no systemic upset
- Severe: >6 bloody stools per day + features of systemic upset
(Pyrexia, tachycardia, anaemia, raised inflammatory markers)

Inducing remission:

Treatment depends on the extent and severity of disease

1) Rectal (topical) aminosalicylates or steroids:

- ✓ For distal colitis----- > rectal **mesalazine** has been shown to be superior to rectal steroids and oral aminosalicylates

2) Oral aminosalicylates

3) Oral prednisolone

- ✓ It is usually used second-line for patients who fail to respond to aminosalicylates.
- ✓ NICE recommend waiting around 4 weeks before deciding if first-line treatment has failed

Severe colitis

- ✓ Should be treated in hospital
- ✓ Intravenous **steroids** are usually given first-line

Maintaining remission:

- 1) Oral aminosalicylates e.g. Mesalazine
- 2) Azathioprine and mercaptopurine
- 3) Methotrexate is **not recommended** for the management of UC (in contrast to CD)
- 4) There is some evidence that probiotics may prevent relapse in mild to moderate disease

Crohn's disease	Ulcerative colitis
<u>Inducing remission:</u> 1) <u>Glucocorticoids</u> ✓ oral, topical or intravenous ✓ are generally used to induce remission ✓ Budesonide is an alternative in a subgroup of patients 2) <u>Enteral feeding with an elemental diet</u> ✓ may be used in addition to or instead of other measures to induce remission, particularly if there is concern regarding the side-effects of steroids (for example in young children) 3) <u>5-ASA drugs (e.g. mesalazine)</u> ✓ are used second-line to glucocorticoids but are not as effective 4) <u>Azathioprine or mercaptopurine</u> ✓ may be used as an add-on medication to induce remission but is not used as monotherapy ✓ Methotrexate is an alternative to azathioprine ✓ assess thiopurine methyltransferase (TPMT) activity before offering azathioprine or mercaptopurine 5) <u>Infliximab</u> ✓ is useful in refractory disease and fistulating Crohn's ✓ Patients typically continue on azathioprine or methotrexate 6) <u>metronidazole</u> is often used for isolated peri-anal disease	<u>Inducing remission:</u> Treatment depends on the extent and severity of disease 1) <u>rectal (topical) aminosalicylates or steroids:</u> ✓ For distal colitis <u>rectal mesalazine</u> has been shown to be superior to rectal steroids and oral aminosalicylates 2) <u>Oral aminosalicylates</u> 3) <u>Oral prednisolone</u> ✓ It is usually used second-line for patients who fail to respond to aminosalicylates. ✓ NICE recommend waiting around 4 weeks before deciding if first-line treatment has failed <u>Severe colitis</u> ✓ should be treated in hospital ✓ <u>Intravenous steroids</u> are usually given <u>first-line</u>
<u>Maintaining remission:</u> 1) <u>stopping smoking</u> is a priority (remember: smoking makes Crohn's worse, but may help ulcerative colitis) 2) <u>azathioprine or mercaptopurine</u> is used <u>first-line to maintain remission</u> 3) <u>methotrexate</u> is used <u>second-line</u> 4) <u>5-ASA drugs (e.g. mesalazine)</u> should be considered if a patient has <u>had previous surgery</u> <u>Surgery</u> • around 80% of patients with Crohn's disease will eventually have surgery	<u>Maintaining remission</u> 5) oral aminosalicylates e.g. mesalazine 6) azathioprine and mercaptopurine 7) methotrexate is not recommended for the management of UC (in contrast to Crohn's disease) 8) there is some evidence that probiotics may prevent relapse in patients with mild to moderate disease

Aminosalicylate drugs

- 5-aminosalicylic acid (5-ASA) is released in the colon and is not absorbed.
- It acts locally as an anti-inflammatory.
- The mechanism of action is not fully understood but 5-ASA may inhibit prostaglandin synthesis

1) Sulphasalazine

- a combination of sulphapyridine (a sulphonamide) and 5-ASA
- many side-effects are due to the sulphapyridine moiety:
 - 1) headache,
 - 2) rashes,
 - 3) oligospermia,
 - 4) Heinz body anaemia,
 - 5) megaloblastic anaemia
- other side-effects are common to 5-ASA drugs (see mesalazine)

2) Mesalazine

- a delayed release form of 5-ASA
- sulphapyridine side-effects are avoided

Mesalazine side-effects:

- 1) Headache,
- 2) Agranulocytosis
- 3) GI upset,
- 4) Pancreatitis: 7 times more common in patients taking mesalazine than sulfasalazine
- 5) Interstitial nephritis

3) Olsalazine

- two molecules of 5-ASA linked by a diazo bond, which is broken by colonic bacteria

Toxic colonic dilatation

Clinical features: (may be deceptive in patients treated with steroids):

- 1) Colitis - usually severe UC but also with Crohn's colitis and rarely ischaemic or infective colitis
- 2) Pyrexia > 37.8°C
- 3) Neutrophil count > 10 ×10⁹/L
- 4) Heart rate > 90
- 5) Radiological:
 - ☒ Colonic dilatation - widest diameter ≥ 6 cm in the transverse colon.
 - ☒ Other radiological findings include loss of haustral pattern, mucosal oedema and thumbprinting.

Risk factors for the precipitation of toxic colonic dilatation:

- Hypokalaemia, Hypomagnesaemia
 - Under-treatment,
 - Purgative bowel preparations for colonoscopy
 - Non-steroidals, Opioids, Anti-cholinergics, and Anti-diarrhoeal drugs
-
- ☒ The 2007 ECCO guidelines recommend the use of **Truelove-Witts criteria** for classification of disease activity in ulcerative colitis.
 - ☒ The scores use a combination of assessment of degree of mucosal bleeding/diarrhoea and signs of systemic toxicity.
 - ☒ Temperature, frequency of bloody stools, pulse rate, haemoglobin level, and C reactive protein and erythrocyte sedimentation rate are used in combination.
 - ☒ The presence of extra-gastrointestinal manifestations of ulcerative colitis is not used as a marker of severity.
 - ☒ In **Truelove-Witts criteria** severe colitis is defined as:
a bloody stool frequency of > 6 per 24 hours and one of;
 - Pulse >90
 - Temperature >37.8°C
 - Haemoglobin <105 g/L
 - C reactive protein >30 mg/L
 - Erythrocyte sedimentation rate >30 mm/h.

Anal fissure

- A longitudinal or elliptical tears of the squamous lining of the distal anal canal
- If present for less than 6 weeks they are defined as acute
- chronic if present for more than 6 weeks
- Around 90% of anal fissures occur on the posterior midline

Management of an acute anal fissure (< 6 weeks)

- 1) dietary advice: high-fibre diet with high fluid intake
- 2) bulk-forming laxatives are first line - if not tolerated then lactulose should be tried
- 3) lubricants such as petroleum jelly may be tried before defecation
- 4) topical **anaesthetics-analgesia**
 - topical steroids do not provide significant relief

Management of a chronic anal fissure (> 6 weeks)

- 1) the above techniques should be continued
- 2) **topical glyceryl trinitrate** (GTN) is **first line treatment for a chronic anal fissure**
- 3) if topical GTN is not effective after 8 weeks then secondary referral should be considered for **surgery** or **botulinum toxin**

Screen for colorectal cancer in inflammatory bowel disease

- Patients with colitis as part of inflammatory bowel disease are at increased risk of colonic cancer.
- All patients with a diagnosis of colitis should have a screening colonoscopy 10 years after index presentation, preferably when they are in remission.
- The interval between subsequent colonoscopies is dependent upon the presence of risk factors and appearance at colonoscopy.

High risk:

The following features make an individual high risk:

- 1) dysplasia declining surgery or stricture in the last 5 years
- 2) primary sclerosing cholangitis
- 3) first degree relative with colorectal cancer under the age of 50, or
- 4) Extensive colitis with moderate to severe inflammation.

Patients with high risk features should have **yearly** colonoscopy

Intermediate risk:

Patients with inflammatory bowel disease are considered at **intermediate** risk if they have any of:

- 1) extensive mildly active inflammation
- 2) history of colorectal cancer in a first degree relative over 50 or
- 3) Post-inflammatory polyps.

These patients should have **3** yearly colonoscopy

Low risk:

- 1) Individuals with extensive colitis but no active inflammation, only left-sided disease or
- 2) Crohn's colitis affecting <50% of the colon

Low risk and should be offered screening colonoscopy on **5** yearly bases

Colectomy should be considered where surveillance endoscopy reveals high-grade dysplasia (in addition to where it is appropriate for the treatment of malignancy).



Sigmoid volvulus

The loop of sigmoid colon has a classical bean shape, with the apex over the S2/3 junction in the left iliac fossa with the loop of sigmoid colon distending covering the liver and descending colon.

The most important feature of a sigmoid volvulus rather than a large redundant distended loop of sigmoid colon is the absence of haustra

Malabsorption

- Malabsorption is characterised by diarrhoea, steatorrhoea and weight loss.
- Causes may be broadly divided into **intestinal** (e.g. villous atrophy), **pancreatic** (deficiency of pancreatic enzyme production or secretion) and **biliary** (deficiency of bile-salts needed for emulsification of fats)

1) Intestinal causes of malabsorption:

- coeliac disease
- Crohn's disease
- tropical sprue
- Whipple's disease
- **Giardiasis**
- brush border enzyme deficiencies (e.g. lactase insufficiency)

2) Pancreatic causes of malabsorption:

- chronic pancreatitis
- cystic fibrosis
- pancreatic cancer

3) Biliary causes of malabsorption:

- biliary obstruction
- primary biliary cirrhosis

4) Other causes:

- bacterial overgrowth (e.g. systemic sclerosis, diverticulae, blind loop)
- short bowel syndrome
- lymphoma

Whipple's disease

- A rare multi-system disorder caused by **Tropheryma whippelii** infection.
- It is more common in those who are **HLA-B27** positive and in **middle-aged men**

Features: male > female 9: 1

- 1) malabsorption: diarrhoea, weight loss, hypocalcaemia, vitamin deficiency (A,C)
- 2) large-joint **arthralgia**, clubbing
- 3) **lymphadenopathy**
- 4) skin: **hyperpigmentation** and **photosensitivity**
- 5) perioral and malar hyperpigmentation
- 6) pleurisy, pericarditis, myocarditis, It valve lesion
- 7) neurological symptoms (rare):
 - ✓ ophthalmoplegia,
 - ✓ ataxia
 - ✓ dementia,
 - ✓ seizures,
 - ✓ myoclonus

Investigation:

- jejunal biopsy shows deposition of macrophages containing **Periodic acid-Schiff (PAS)** granules
- The diagnosis is made by demonstrating the presence of **T. whippelii DNA** in tissue by **PCR**.

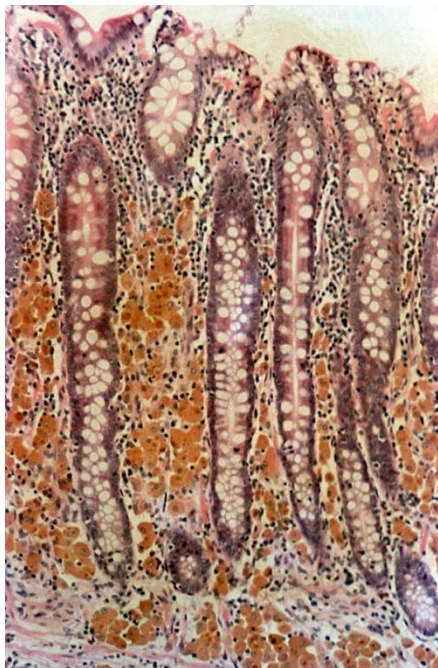
Management:

- guidelines vary:
 - ✓ **IV penicillin** plus **streptomycin 2 weeks** then
 - ✓ oral **co-trimoxazole** or **tetracyclin** for a year (have the lowest relapse rate)

.....ستريم لمدة سنة

Melanosis coli

- Melanosis coli is a disorder of pigmentation of the bowel wall.
- Histology demonstrates **pigment-laden macrophages**
- It is associated with laxative abuse, especially anthraquinone compounds such as senna
- Melanosis coli is a histological diagnosis made from rectal biopsy material which shows numerous macrophages filled with **brown pigment** within the **lamina propria**.
- This phenomenon is seen in over 70% of persons who use anthraquinone laxatives (for example, cascara sagrada, senna, and frangula) within several months of use.
- The condition is benign and reversible on stopping the laxatives.
- The macroscopic appearance varies from deep black pigmentation to reticulated brown discolouration.
- Melanosis coli may involve the entire large intestine, but can be segmental.
- The discolouration is caused by deposits of **lipofuscin** rather than true melanin deposition.
- Anthraquinone cathartics induce **apoptosis** of epithelial cells of large intestine. The apoptotic bodies are taken up by epithelial macrophages and they are converted to **lipofuscin**.



Bile-acid malabsorption (excess bile)

- Bile-acid malabsorption is a cause of **chronic watery diarrhoea**.
- This may be:
Primary, due to an excessive production of bile acid, or
Secondary to an underlying gastrointestinal disorder causing reduced bile acid absorption
- Secondary causes are often seen in patients with ileal disease, such as with **Crohn's**.

Other secondary causes include: ----- >CCCS

- 1) coeliac disease
- 2) cholecystectomy
- 3) small intestinal bacterial overgrowth

Investigation:

- the test of choice is **SeHCAT**
 - ✓ **nuclear medicine test using a gamma-emitting selenium molecule** in selenium homocholic acid taurine or tauroselcholic acid (SeHCAT)
 - ✓ scans are done 7 days apart to assess the retention/loss of radiolabelled ⁷⁵SeHCAT

Management:

- bile acid sequestrants e.g. cholestyramine

Small bowel bacterial overgrowth syndrome

(SBBOS)

Excessive amounts of bacteria in small bowel resulting in gastrointestinal symptoms.

Risk factors for SBBOS

- neonates with congenital GI abnormalities, diverticulae, blind loop
- scleroderma
- DM
- stricture, adhesions & fistula (between small & large bowel)

It should be noted that many of the features overlap with irritable bowel syndrome:

- chronic diarrhoea
- bloating, flatulence
- abdominal pain

Bacterial overgrowth investigation:

- The gold standard of bacterial overgrowth is small bowel aspiration and culture.
- **high or normal folate, low B12** (bacterial metabolism of B12 to folate)

Other possible investigations include:

- ✓ hydrogen breath test
- ✓ 14C-xylose breath test
- ✓ 14C-glycocholate breath test: used increasingly less due to low specificity
- In practice many clinicians give an empirical course of antibiotics as a trial

Management:

- correction of underlying disorder
- antibiotic therapy:
 - ✓ **Rifaximin** is now the treatment of choice due to relatively low resistance (also used now in hepatic encephalopathy).
 - ✓ **Co-amoxiclav** or **metronidazole** are also effective in the majority of patients.

Villous adenoma

- Colonic polyps with the potential for malignant transformation.
- They characteristically secrete large amounts of mucous, potentially resulting in electrolyte disturbances.
- The vast majority are asymptomatic.

Possible features:

- 1) Non-specific lower gastrointestinal symptoms
- 2) Secretory diarrhoea may occur
- 3) Microcytic anaemia
- 4) Hypokalaemia

hypokalemia & hyponatremia..... تذكر انها من اسباب Villous adenomas

VIPoma

- VIP (vasoactive intestinal peptide)
- Source: small intestine, pancreas
- Stimulation: neural
- Actions:
 - 1) stimulates secretion by pancreas and intestines,
 - 2) inhibits acid and pepsinogen secretion

VIPoma:

- 90% arise from pancreas
- large volume diarrhea → weight loss, dehydration, hypokalaemia, hypochlorhydria (WDHH)

Colorectal cancer

- Colorectal cancer is the third most common type of cancer in the UK and the second most cause of cancer deaths
- Location of cancer (averages)**
 - ☒ Rectal: ----- 40%
 - ☒ Sigmoid: ----- 30%
 - ☒ Ascending colon and caecum: 15%
 - ☒ Transverse colon: ----- 10%
 - ☒ Descending colon: ----- 5%
- It is currently thought there are three types of colon cancer:
 - 1) Sporadic (**95%**)
 - 2) Hereditary non-polyposis colorectal carcinoma (HNPCC, **5%**)
 - 3) Familial adenomatous polyposis (FAP, **<1%**)

Sporadic

- Studies have shown that sporadic colon cancer may be due to a series of genetic mutations.
- For example, more than **half** of colon cancers show allelic loss of the **APC gene** (adenomatous polyposis coli gene).
- It is believed a further series of gene abnormalities e.g.
 - ☒ activation of the **K-ras oncogene**,
 - ☒ **deletion of p53 and DCC tumour suppressor genes** lead to invasive carcinoma (**Cetuximab acts on Kras receptors**)

Hereditary non-polyposis colorectal carcinoma

HNPCC

- An **autosomal dominant** condition
- The most common form of inherited colon cancer.
- Around 90% of patients develop cancers, often of the proximal colon, which are usually poorly differentiated and highly aggressive.
- Currently seven mutations have been identified
- Mutations affect genes involved in **DNA mismatch repair** leading to **microsatellite instability**.
- The most common genes involved are:
 - MLH1 (30%) ملح 1
 - MSH2 (60% of cases) مش 2
- Patients with HNPCC are also at a higher risk of other cancers, with **endometrial cancer** being the next most common association, after colon cancer. also **ovarian cancer** سؤال الامتحان الاول

The Amsterdam criteria are sometimes used to aid diagnosis:

- 1) at least 3 family members with colon cancer
- 2) the cases span at least two generations
- 3) at least one case diagnosed before the age of 50 years

Familial adenomatous polyposis FAP

- A rare **autosomal dominant** condition
- Leads to the formation of hundreds of polyps by the age of 30-40 years.
- Patients inevitably develop carcinoma.
- It is due to a mutation in a tumour suppressor gene called **adenomatous polyposis coli gene** (APC), located on **chromosome 5**.
- Genetic testing can be done by analysing DNA from patient's WBCs.
- Patients generally have a **total colectomy** with **ileo-anal pouch** formation in their twenties.
- Patients with FAP are also at risk from **duodenal tumours**.

Gardner's Syndrome: A variant of FAP can also feature:

- 1) osteomas of the skull and mandible,
- 2) retinal pigmentation,
- 3) thyroid carcinoma and
- 4) epidermoid cysts on the skin

Colorectal cancer referral guidelines:

NICE recommend the following patients are referred **urgently** (i.e. within 2 weeks) to colorectal services for investigation:

- 1) patients **> 40 years** old,
 - ⇒ reporting rectal bleeding with a change of bowel habit towards looser stools and/or increased stool frequency persisting for **6 weeks** or more
- 2) patients **> 60 years** old,
 - ⇒ With rectal bleeding persisting for **6 weeks** or morewithout a change in bowel habit and without anal symptoms
 - Or**
 - ⇒ with a change in bowel habit to looser stools and/or more frequent stools persisting for 6 weeks or morewithout rectal bleeding
- 3) **any patient** presenting with a **right lower abdominal mass** consistent with involvement of the large bowel
- 4) **any patient** with a palpable **rectal mass**
- 5) **unexplained iron deficiency** anaemia in men or non-menstruating women
(Hb < 11 g/dl in men, < 10 g/dl in women)

Colorectal cancer screening:

- Most cancers develop from adenomatous polyps.
- Screening for colorectal cancer has been shown to reduce mortality by 16%
- The NHS now has a national screening programme offering screening **every 2 years** to all men and women aged **60 to 74 years**. Patients aged over 74 years may request screening
- eligible patients are sent **faecal occult blood** (FOB) tests through the post every 2 years
- patients with abnormal results are offered a **colonoscopy**
- **A single positive result** will trigger an invitation to attend a consultation to consider colonoscopy.
- An uncertain or unclear result will result in a request to repeat up to a maximum of two further tests.
- Persistent unclear results require further investigation with consideration of colonoscopy.
- A negative faecal occult blood does not exclude an underlying diagnosis of colorectal cancer.
- Any patient with symptoms, irrespective of a negative faecal occult blood test, should be investigated for the possibility of underlying bowel cancer as appropriate

At colonoscopy, approximately:

- 1) 5 out of 10 patients (**50%**) will have a **normal** (exam $\frac{1}{2}$ of patients)
- 2) 4 out of 10 patients (**40%**) will be found to have **polyps** which may be removed due to their premalignant potential
- 3) 1 out of 10 patients (**10%**) will be found to have **cancer**

The interval between surveillance colonoscopies:

It is determined by the risk of that individual developing a neoplastic lesion.

- When a colonoscopy has been performed (and in the absence of other risk factors for bowel cancer, for example, personal history, significant family history, predisposing disease) it is the appearance of polyps at colonoscopy that determines the intervals between screenings.
 - Risk is determined based upon the number and size of polyps found;
- 1) Patients with ≤ 2 polyps, both < 1 cm have a **low risk** of cancer
 $\Rightarrow$ **Do not require further routine surveillance**
 - 2) A patient with 3-4 small adenomas or any one adenoma > 1 cm is at least **intermediate risk**
 $\Rightarrow$ Should have a further colonoscopy in **3 years**
 - 3) **High risk** patients are those with ≥ 5 small adenomas or ≥ 3 where one is > 1 cm
 $\Rightarrow$ Should have a further colonoscopy in **1 year**

The interval to the next colonoscopy is determined by the findings of the most recent investigation.

- 1) A low risk patient with a negative test
⇒ **Should not** have further routine colonoscopy booked
- 2) An intermediate risk patient with a follow-up negative examination
⇒ **Should** have another colonoscopy in **3 years** before surveillance is stopped
- 3) Even following a negative or low-risk follow up colonoscopy patients with **high-risk** findings on their initial test
⇒ **Should** subsequently be managed as intermediate risk

- Polyps that are ≤ 1 cm in size $\Rightarrow$ can be removed in a single go with biopsy forceps or snares.
- The need for repeat colonoscopy following polypectomy applies to large sessile adenomas removed piecemeal (that is, multiple snares required).
- Small areas of residual polyp can then be treated endoscopically, with a further check for complete eradication in two to three months. India ink tattooing aids recognition of the polypectomy site at follow up.
- If extensive residual polyp is seen, surgical resection needs to be considered. If there is complete healing of the polypectomy site, then there should be a colonoscopy at one year, to check for missed synchronous polyps, before returning to three yearly surveillance

Staging Colorectal Cancer:

The Dukes' staging system has now largely been replaced with the TNM system, however it is still used and referred to in follow up of patients diagnosed and treated recently.

It is classified as following:

- 1) Dukes' A: Carcinoma in situ limited to **mucosa** or **submucosa**,
⇒ **surgery only**
- 2) Dukes' B: Invasion through **the bowel wall** but **not involving lymph nodes**
⇒ **surgery then**
⇒ **radiotherapy**
- 3) Dukes' C: **Involvement of lymph nodes** (C1 < 3 LN)
⇒ **surgery plus chemotherapy** &
⇒ radiotherapy may be needed
- 4) Dukes' D: Widespread metastases.
⇒ Surgery to remove the tumour or to bypass an obstructing tumour,
⇒ **palliative** chemotherapy and/or radiotherapy for symptom relief;

5 years survival:

- Dukes' A: **>90%**
- Dukes' B: **>70%**
- Dukes' C: **50%**
- Dukes' D: **5%**

The treatment of colorectal cancers depends upon the stage:

Stage I (Duke's A):

- Carcinoma in situ limited to mucosa or submucosa (T1, N0, M0)
- Standard treatment involves surgery to remove the tumour.
- Additional treatments are not usually needed.
- For Duke's stage A tumours involving only the mucosa, the five year survival rate exceeds 90%.

Stage II (Duke's B):

- Cancer that extends into the muscularis (B1), into or through the serosa (B2).
- Standard treatment is:
 - 1) surgical removal of the tumour followed by radiotherapy
 - 2) Radiotherapy has been shown to reduce the rate of recurrence.
 - 3) The role of adjuvant chemotherapy is less clear in Duke's B than in Duke's C
- Patients may be offered the opportunity of entering into a clinical trial of chemotherapy, but chemotherapy is not typically given as standard.
- For Duke's stage B colon cancers, the five year survival rate is greater than 70% and can be greater than 80% if the tumour does not penetrate the muscularis mucosa.

Stage III (Duke's C):

- Cancer that extends to regional lymph nodes (T1-4, N1, M0).
- Treatment involves:
 - 1) Surgery to remove the tumour,
 - 2) chemotherapy with **5-FU** and **leucovorin** and
 - 3) in some patients radiotherapy may also be needed (especially if the tumour is large and invading the tissue surrounding the colon)
- The five year survival rate for Duke's C is 50%.

??There is no role for adjuvant radiation therapy in patients with colon cancer. Adjuvant radiotherapy is useful in patients with rectal cancer in whom the risk for local recurrence is greater (from onexam).

Stage IV (Duke's D):

- Cancer that has metastasised to distant sites (T1-4, N1-3, M1).
- Treatment involves:
 - 1) Surgery to remove the tumour or to bypass an obstructing tumour,
 - 2) Palliative chemotherapy and/or radiotherapy for symptom relief; use of new agents such as:
 - ⇒ **cetumixab** (a recombinant human/mouse chimeric epidermal growth factor inhibitor) or
 - ⇒ **becavizumab** (a recombinant human anti-vascular epidermal growth factor (VEGF) antibody).
- Five year survival is approximately 5%.

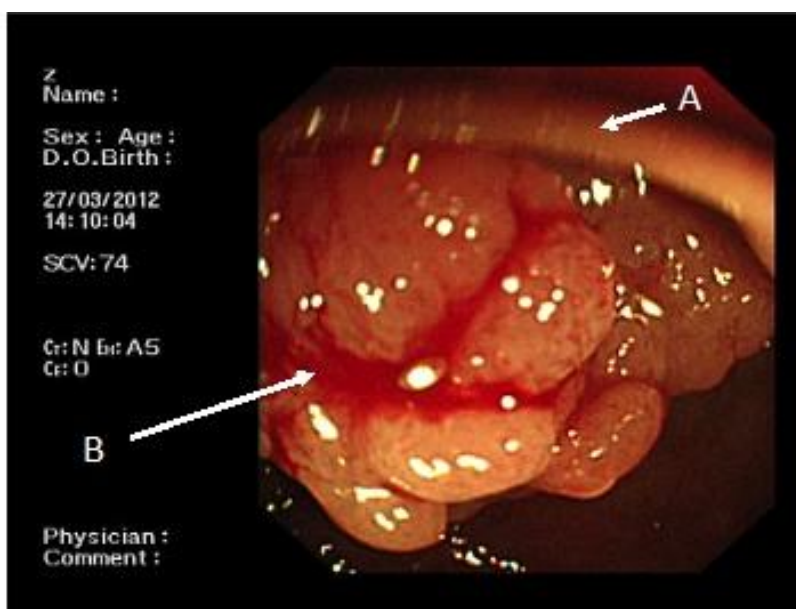
Metastatic disease following curative surgery for colon cancer:

- 20% - 30% of patients with metastatic disease following curative surgery for colon cancer will have isolated hepatic metastases.
- Surgical resection is potentially curative in 25%.

Contraindications to resection include

- 1) Tumours that are too large
- 2) Multiple tumours
- 3) Unfavorable anatomic location
- 4) Poor hepatic function and
- 5) Poor performance status.

However, even in patients who are not candidates for surgical resection of hepatic metastases, chemotherapy may convert previously inoperable lesions into lesions amenable to surgery.



A large bowel haustral fold can be seen at the top of the picture (A) and beyond this protruding into the lumen is a large, irregular polypoid mass with a friable surface and evidence of bleeding (B). Appearances are consistent with a **colorectal cancer**.

Peutz-Jeghers syndrome

- an **autosomal dominant** condition
- characterised by:
 - 1) numerous hamartomatous polyps in the gastrointestinal tract
 - 2) pigmented freckles on the lips, face, palms and soles
- Around 50% of patients will have died from a GIT cancer by the age of 60 years.

Genetics:

- autosomal dominant
- responsible gene encodes **serine threonine kinase** LKB1 or STK11

Features:

- 1) hamartomatous polyps in GIT (mainly small bowel)
- 2) pigmented lesions on lips, oral mucosa, face, palms and soles
- 3) **intestinal obstruction** e.g. intussusception
- 4) GI **bleeding**
- 5) There is an ASSOCIATION with **non-GIT** malignancies such as **endometrial**, **ovarian** and **lung**.

Management:

- conservative unless complications develop
- **Colonoscopy** every **2 years** after the age of 25 years for evaluation of the presence of polyps and polypectomy.



Gastroenteritis

- Gastroenteritis may either occur whilst at home or whilst travelling abroad (travellers' diarrhoea)

Travellers' diarrhoea:

- May be defined as at **least 3 loose to watery stools in 24 hours** with or without one or more of:
 - ✓ Abdominal cramps,
 - ✓ fever,
 - ✓ nausea, vomiting or
 - ✓ Blood in the stool.
- The most common cause is **Escherichia coli**

Acute food poisoning:

- This describes the sudden onset of nausea, vomiting and diarrhoea after the ingestion of a toxin.
- Acute food poisoning is typically caused by Staph aureus, Bacillus cereus or Clostridium perfringens.

Stereotypical histories

Infection	Typical presentation
Escherichia coli	- Common amongst travelers - Watery stools - Abdominal cramps and nausea
Amoebiasis	- Gradual onset bloody diarrhoea, - abdominal pain and tenderness which may last for several weeks
Giardiasis	Prolonged, non-bloody diarrhea
Cholera	- Profuse, watery diarrhea - Severe dehydration resulting in weight loss - Not common amongst travelers
Shigella	Bloody diarrhoea, - Vomiting and abdominal pain
Staphylococcus aureus S—S—S	- Severe vomiting - Short incubation period
Campylobacter	- A flu-like prodrome is usually followed by crampy abdominal pains, - fever and diarrhoea which may be bloody - Complications include Guillain-Barre syndrome - Reiter s syndrome (cannot pee ,cannot see ,cannot climb the tree)
Bacillus cereus	- Two types of illness are seen: 1) vomiting within 6 hours, stereotypically due to rice 2) diarrhoeal illness occurring after 6 hours - associated with chinese food

Incubation period:

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- 1-6 hrs: Staph. aureus, Bacillus cereus**vomiting subtype ,diarrhoeal illness IP of 6-14 hrs
- 12-48 hrs: Salmonella, E. coli
- 48-72 hrs: Shigella, Campylobacter
- > 7 days: Giardiasis, Amoebiasis

Mesenteric ischaemia

- Mesenteric ischaemia is primarily caused by **arterial embolism** resulting in infarction of colon.
- It is more likely to occur in areas such as the **splenic flexure** that are located at the borders of the territory supplied by the superior and inferior mesenteric arteries.

Predisposing factors:

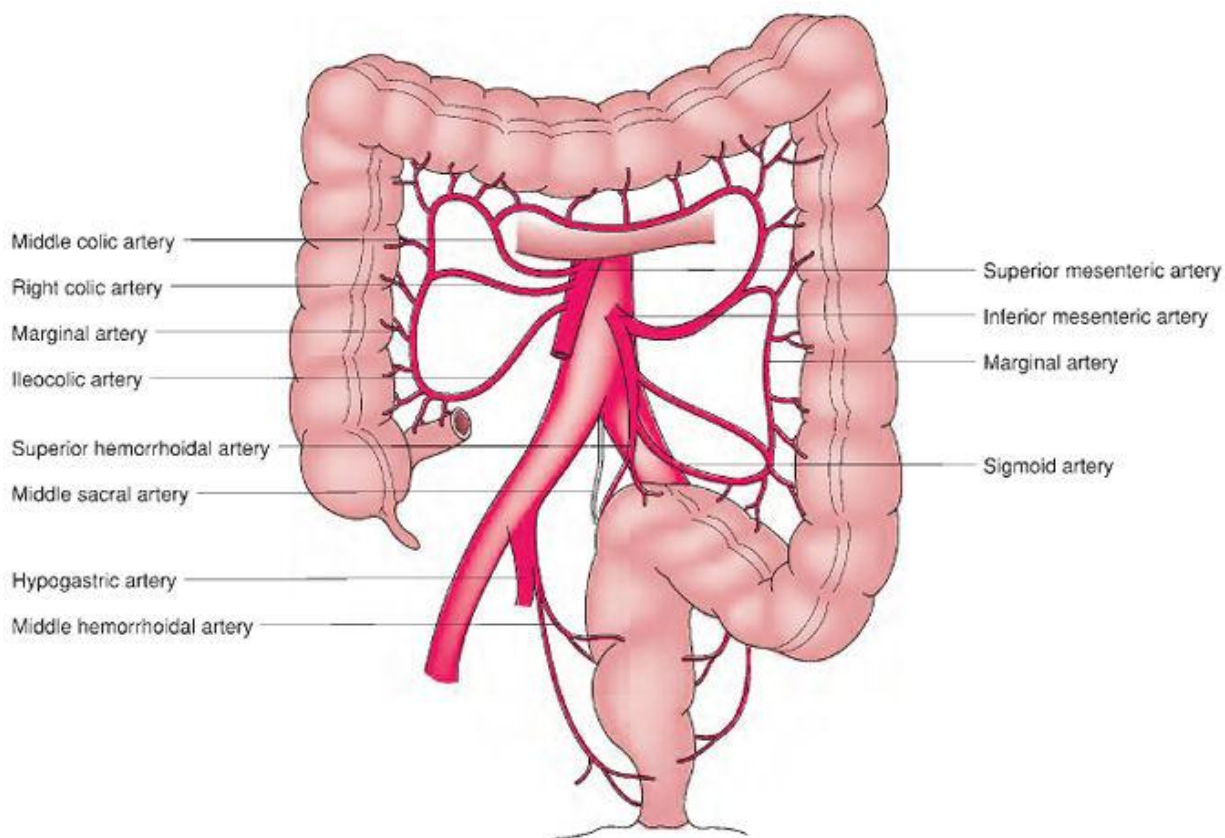
- Increasing age
- Atrial fibrillation, other causes of emboli: endocarditis
- Cardiovascular disease risk factors: smoking, hypertension, diabetes

Features:

- 1) Abdominal pain
- 2) Rectal bleeding
- 3) Diarrhoea
- 4) Fever
- 5) Bloods typically show an elevated WBC associated with acidosis

Management:

- supportive care----- >laparotomy and bowel resection



Clostridium difficile

- Clostridium difficile is a **Gram positive rod** often encountered in hospital practice.
- It produces an exotoxin which causes intestinal damage leading to a syndrome called pseudomembranous colitis.
- CD develops when the normal gut flora are suppressed by broad-spectrum antibiotics.
- Clindamycin is historically associated with causing Clostridium difficile but the aetiology has evolved significantly over the past 10 years.
- Second and third generation cephalosporins are now the leading cause of CD.

Features:

- 1) Diarrhoea **up to 10 weeks** after antibiotic therapy
- 2) Abdominal pain
- 3) A **raised WBC count** is characteristic
- 4) If severe **toxic megacolon** may develop

Diagnosis: is made by detecting Clostridium difficile **toxin** (CDT) in the stool

Management:

- 1) first-line therapy is oral metronidazole for 10-14 days
- 2) if severe or not responding to metronidazole then oral vancomycin may be used
- 3) for life-threatening infections a combination of oral vancomycin and intravenous metronidazole should be used

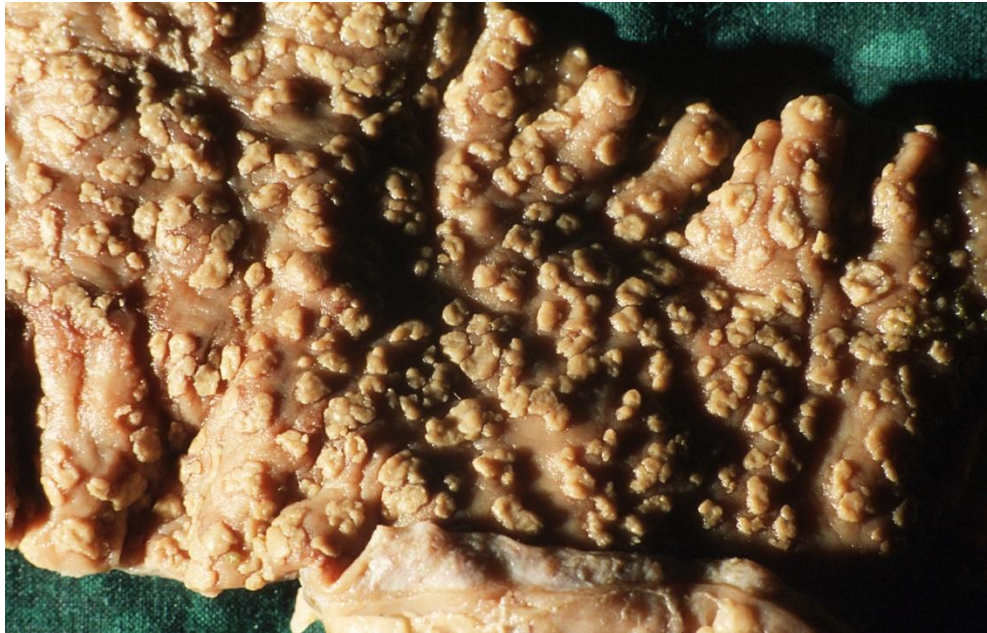


Elderly lady with infectious colitis secondary to Clostridium difficile. On the abdominal film note the loss of bowel wall architecture and thumb-printing consistent with colitis.

The CT from the same patient is enhanced by oral contrast. There is moderate free fluid in pelvis and peritoneum. The colon is oedematous throughout with enhancing walls, but of normal calibre. The sigmoid colon is smooth and featureless. Small bowel, liver, spleen, kidneys, adrenals and pancreas are normal.

In **severe** disease the superiority of vancomycin over metronidazole was demonstrated

- > 60 yrs
- Temperature >38.3°C
- WBC >15 ×10⁹/L - Albumin <25 g/L
- Endoscopic evidence of **pseudomembranous colitis** and
- **ICU** admission (haemodynamically unstable)



The picture shows a thick pseudomembrane adherent to the colonic mucosa



The AXR suggests a colitic process (thickened mucosa with thumb printing) particularly around the area of the splenic flexure and below.

These appearances are highly suggestive of an ischaemic colitis but other causes would need to be excluded, for example, infective colitis (including *Clostridium*), ulcerative colitis and radiation colitis (usually suggested by the history).

Flexible sigmoidoscopy would be the best investigation - safer than colonoscopy (relative contraindication in active colitis), allowing biopsies to be taken and the viewing of a possible pseudomembrane. Occasionally the mucosa has a characteristic appearance.

Ischaemic colitis is more common in elderly arteriopaths with pain as a predominant feature.

Meckel's diverticulum

- Meckel's diverticulum is the vestigial remnant of the omphalomesenteric duct.
- It is normally located in the terminal ileum within ~60 cm of the ileocaecal valve and it averages 6 cm in length.
- About 50% of these contain **ectopic gastric mucosa**, commonly leading to clinical presentations of peptic ulceration and haemorrhage.

Other complications of Meckel's diverticulum include

- 1) Diverticulitis
- 2) Intussusception
- 3) Perforation
- 4) Obstruction.

Although it occurs much more commonly in children it is an important differential consideration for gastrointestinal bleed in adults.

Tc-99m pertechnetate accumulates in gastric mucosa and is the study of choice for identifying ectopic gastric mucosa in a Meckel's diverticulum.



The picture shows an excised Meckel's diverticulum.

Malnutrition

- Malnutrition is an important consequence of and contributor to chronic disease.
- It is clearly a complex and multifactorial problem that can be difficult to manage but there are a number of key points to remember for the exam.

NICE define malnutrition as the following:

- a Body Mass Index (BMI) < 18.5;
Or
 - unintentional weight loss > 10% within the last 3-6 months;
Or
 - BMI < 20 and unintentional wt loss > 5% within the last 3-6 months
- Around 10% of patients aged over 65 years are malnourished, the vast majority of those living independently, i.e. not in hospital or care/nursing homes.
 - Screening for malnutrition is mostly done using **MUST** (Malnutrition Universal Screen Tool).
 - It should be done on admission to care/nursing homes and hospital, or if there is concern. For example an elderly, thin patient with pressure sores
 - it takes into account BMI, recent weight change and the presence of acute disease
 - categorizes patients into low, medium and high risk

Management of malnutrition is difficult. NICE recommend the following points:

- dietician support if the patient is high-risk
- a 'food-first' approach with clear instructions (e.g. 'add full-fat cream to mashed potato'), rather than just prescribing oral nutritional supplements (ONS) such as Ensure
- if ONS are used they should be taken between meals, rather than instead of meals

علاج سوء التغذية هو (الطعام اولا) والمكملات الغذائية تكون بين الوجبات وليست بديلا للطعام.....

Refeeding syndrome

- Refeeding syndrome describes the metabolic abnormalities which occur on feeding a person following a period of starvation.

The metabolic consequences include:

- 1) Hypophosphataemia.
- 2) Hypokalaemia.
- 3) Hypomagnesaemia.
- 4) Abnormal fluid balance.

These abnormalities can lead to organ failure.

Prevention:

- NICE produced guidelines in 2006 on nutritional support.
- Refeeding syndrome may be avoided by identifying patients at a high-risk of developing refeeding syndrome:

Patients are considered high-risk:

If one or more of the following:

- BMI < 16 kg/m²
- Unintentional weight loss >15% over 3-6 months
- Little nutritional intake > 10 days
- Hypokalaemia, hypophosphataemia or hypomagnesaemia prior to feeding

If two or more of the following:

- BMI < 18.5 kg/m²
- unintentional weight loss > 10% over 3-6 months
- little nutritional intake > 5 days
- history of:
 - ✓ alcohol abuse,
 - ✓ drug therapy including insulin, chemotherapy, diuretics and antacids

NICE recommend that if a patient hasn't eaten for > 5 days, aim to re-feed at no more than **50% of requirements for the first 2 days.**

Signs & symptoms of the different grades of hypovolaemic shock

Grade 1:

- Up to about **15%** loss of effective blood volume (**~750ml** in an average adult assumed to have a blood volume of 5 litres),
- Mild resting tachycardia and can be well tolerated in otherwise healthy individuals.
- In the elderly or those with conditions such as IHD the additional myocardial oxygen demands may not be tolerated so well.

Grade 2:

- Between **15-30%** loss of blood volume (**750-1500ml**)
- It will provoke a moderate tachycardia and begin to narrow the pulse pressure.
- The capillary refill time will be extended.

Grade 3:

- At **30 - 40%** loss of effective blood volume (**1500 - 2000 ml**)
- The compensatory mechanisms begin to fail and hypotension, tachycardia and low urine output (**<0.5ml/kg/hr in adults**) are seen.

Grade 4:

- At **40-50%** loss of blood volume (**2000-2500 ml**)
- Profound hypotension will develop and if prolonged will cause end-organ damage and death.

Skin disorders associated with malignancy

Paraneoplastic syndromes associated with internal malignancies:

Skin disorder	Associated malignancies
Tylosis	Oesophageal cancer
Acanthosis nigricans	Gastric cancer
Migratory thrombophlebitis	Pancreatic cancer
Necrolytic migratory erythema	Glucagonoma
Acquired hypertrichosis lanuginosa	Gastrointestinal and lung cancer
Dermatomyositis	Ovarian and lung cancer
Erythema gyratum repens	Lung cancer
Pyoderma gangrenosum (bullous and non-bullous forms)	Myeloproliferative disorders
Sweet's syndrome	Haematological malignancy e.g. Myelodysplasia - tender, purple plaques
Acquired ichthyosis	Lymphoma
Erythroderma	Lymphoma

- Lymphoma :----> Erythroderma.....Acquired ichthyosis
- Lung cancer--->Dermatomyositis---Erythema gyratum repens---Acquired hypertrichosis lanuginosa,
- Gastric cancer-----> Acanthosis nigricans
- Oesophageal cancer---> Tylosis
- Pancreatic cancer-----> Migratory thrombophlebitis
- Glucagonoma-----> Necrolytic migratory erythema
- Ovarian-----> Dermatomyositis---
- Haematological malignancy (e.g. Myelodysplasia) --- >Sweet's syndrome (tender, purple plaques)
- Myeloproliferative disorders-----> Pyoderma gangrenosum

Delirium tremens

- The most severe form of alcohol withdrawal.
- Onset is typically three to seven days after cessation of chronic alcohol ingestion.
- It is characterised by:
 - 1) **visual hallucinations**, **مهاله**
 - 2) autonomic instability (tachycardia, hypertension, and pyrexia),
 - 3) obtundation and confusion.
 - 4) Sweating, tremors and agitation.

Hepatic encephalopathy

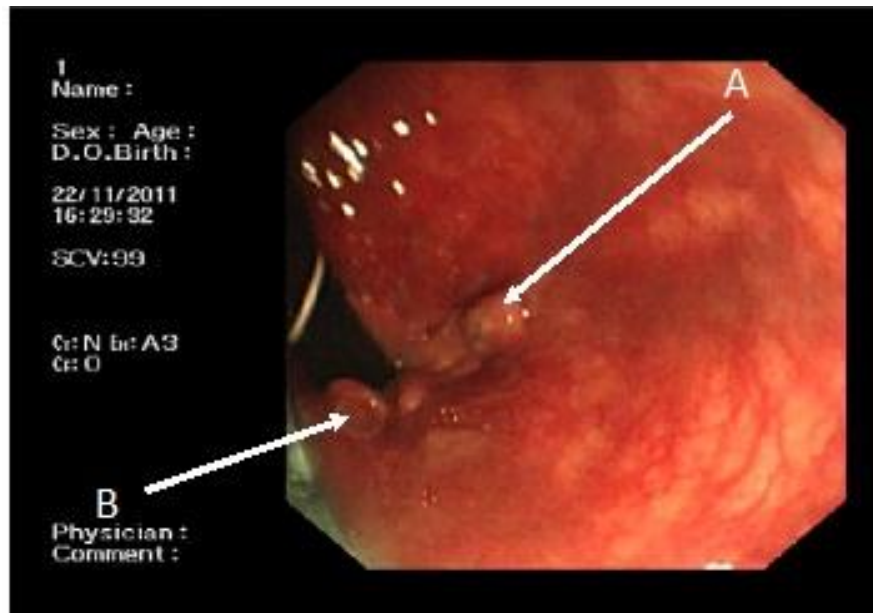
- Tends to be characterised more by drowsiness and obtundation.
- asterixis

Opiate withdrawal

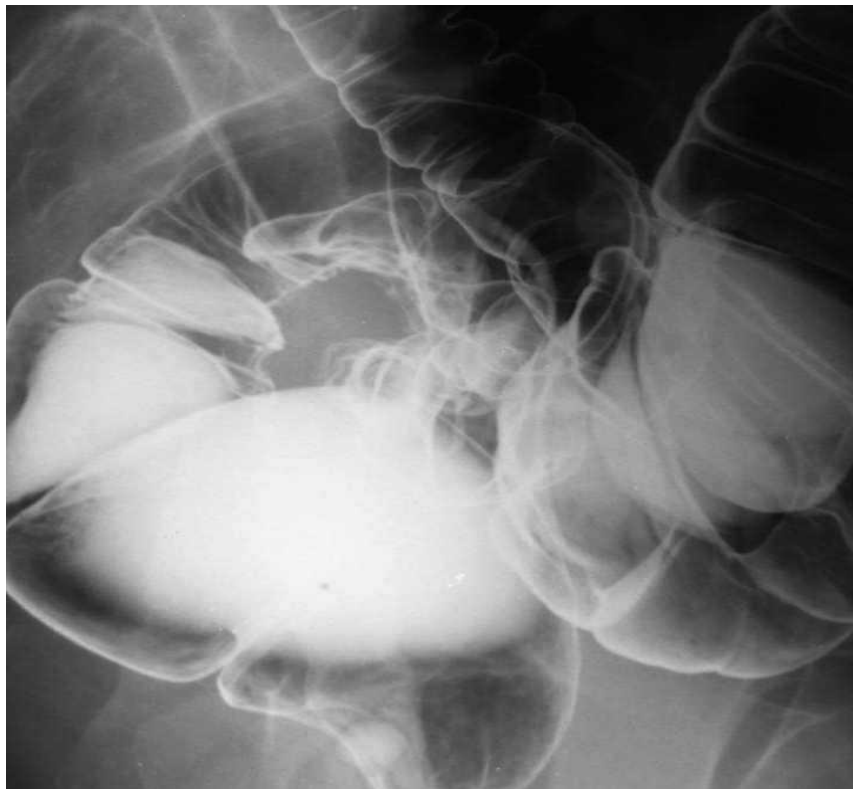
- characterised by diaphoresis, shaking, cramping, agitation and diarrhoea.
- Autonomic instability and hallucinations are not features of opiate withdrawal.

Korsakoff's psychosis

- A chronic condition resulting from untreated thiamine deficiency
- Characterized by both anterograde and retrograde amnesia with confabulation.



The picture is taken with the endoscope retroflexed in the rectum looking towards the anus (the insertion tube can be seen in the 9 o'clock position). The endoscopic picture demonstrates a **haemorrhoid** (A) and a skin tag (B).



Endometriosis

This is responsible for the crenulated appearance to the inferior surface of the sigmoid colon due to extrinsic involvement by endometriosis, which is causing a degree of tethering of the colon and subsequent cyclical rectal bleeding.